

13

British Heart Journal

Monthly journal of cardiology
published in association with
British Cardiac Society

Editorial strategies for preventing and screening for coronary heart disease *M F Oliver*
Myocardial infarction and thrombolysis
electrocardiographic short term and long term results using precordial mapping *R von Essen, W Schmidt, R Uebis, B Edelmann, S Effert, J Silny, G Rau*

Rupture of the myocardium: occurrence and risk factors *M Dellborg, P Held, K Swedberg, A Vedin*
Effect of xamoterol (ICI 118587), a new beta₁ adrenoceptor partial agonist, on resting haemodynamic variables and exercise tolerance in patients with left ventricular dysfunction *A O Molajo, D H Benjett*

How important is a history of chest pain in determining the degree of ischaemia in patients with angina pectoris? *A A Quyyumi, C M Wright, L J Mockus, K M Fox*

Ischaemic heart disease and prodromes of sudden cardiac death: is it possible to identify high risk groups for sudden cardiac death? *J K Madsen*
Benign coronary perforation during percutaneous transluminal coronary angioplasty *B Meier*
Milrinone in heart failure: acute effects on left ventricular systolic function and myocardial metabolism *A D Timmis, P Smyth, M Monaghan, E Walker, K Daly, A A McLeod, D E Jewitt*

Milrinone in heart failure: effects on exercise haemodynamics during short term treatment *A D Timmis, P Smyth, D E Jewitt*
Nuclear magnetic resonance in hypertrophic cardiomyopathy *M Been, D Kean, M A Smith, R H B Douglas, J J K Best, A L Muir*

Localisation of ventricular septal defects by simultaneous display of superimposed colour Doppler and cross sectional echocardiographic images *E Ortiz, P J Robinson, J E Deanfield, R Franklin, F J Macartney, R K H Wyse*
Cross sectional echocardiographic and angiographic correlation in criss cross hearts *P J Robinson, V Kumpeng, F J Macartney*
Evaluation of an elliptical area technique for calculating mitral blood flow by Doppler echocardiography *S J Goldberg, D F Dickinson, N Wilson*

- 1 Functionless retained pacing leads in the cardiovascular system: a complication of pacemaker treatment *F Zerbe, A Ponizyński, W Dyszkiewicz, A Ziemiański, T Dzięgielewski, H Krug* 76
- 6 Effect of exercise on ventricular response to atrial fibrillation in Wolff-Parkinson-White syndrome *J C P Crick, D W Davies, P Holt, P V L Curry, E Sowton* 80
- 11 Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass: comparison with disopyramide and digoxin in a randomised trial *T J Campbell, T P Gavaghan, J J Morgan* 86
- 17 Factors relating to the development of hypertension after cardiopulmonary bypass *T J Cooper, T H Clutton-Brock, S N Jones, J Tinker, T Treasure* 91
- 22 Effect of beta₁ selective adrenoceptor blockade on physiological response to exercise *N F Gordon, J P van Rensburg, H M S Russell, D L Kawalsky, C P Celliers, J F Celliers, D P Myburgh* 96
- 33 Valve prolapse in Behçet's disease *Shan Lu-Yi, Cui Guang-Gen, Liang Ru-Lian* 100
- 36 Case reports
Diffuse non-specific aortitis with multiple saccular aneurysms and aorto-enteric fistula *A K Mukhopadhyay, P Chopra* 102
- 42 Persistent left sided fifth aortic arch in a neonate *A Cabrera, J Galdeano, I Lekuona* 105
- 48 Transient Q waves followed by left anterior fascicular block during exercise *A G Rebuzzi, F Loperfido, L M Biasucci* 107
- 53 Anomalous origin of the left coronary artery from the pulmonary artery in an adult *T Vesterlund, P E B Thomsen, O K Hansen* 110
- 61 Correspondence 113
- Notices 114
- 68 British Medical Association

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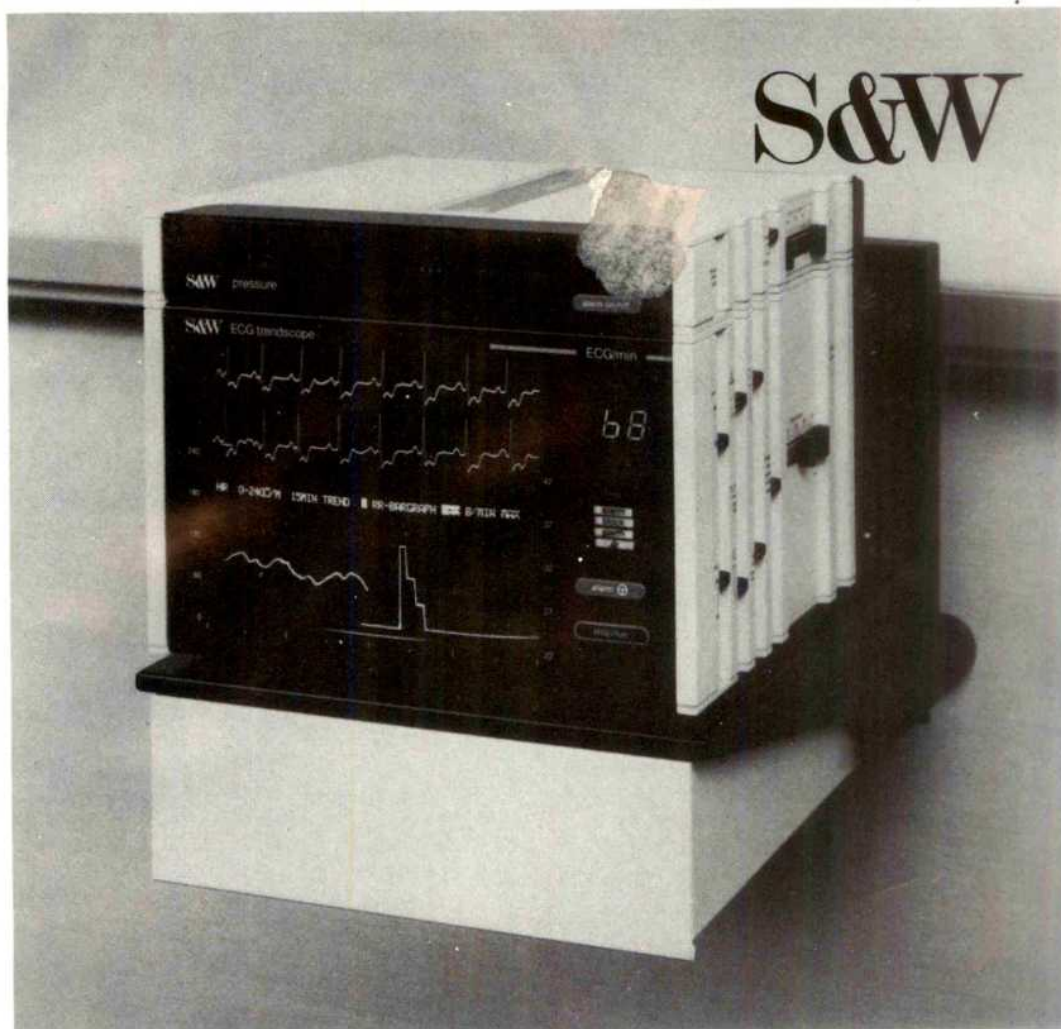
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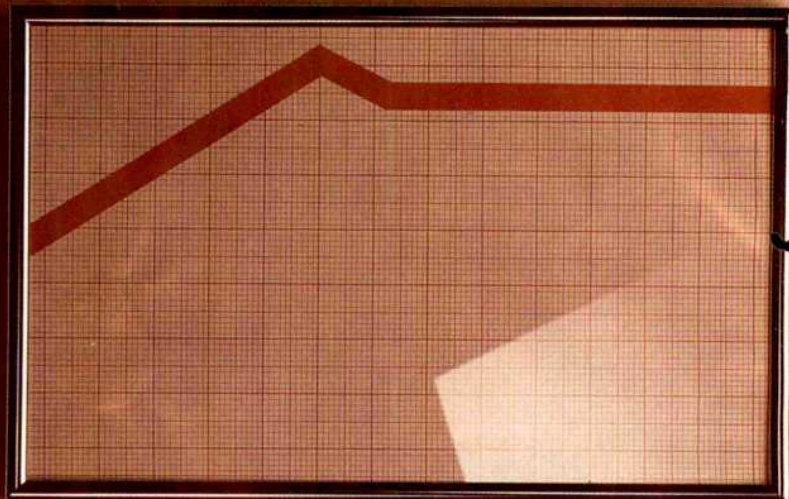
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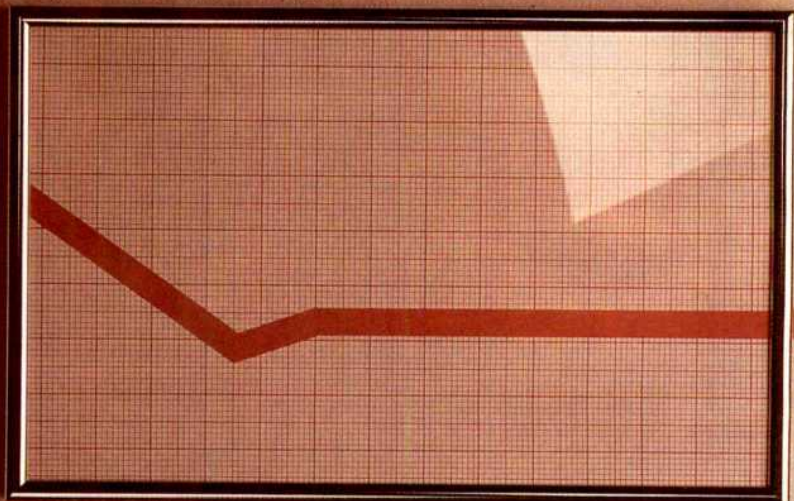
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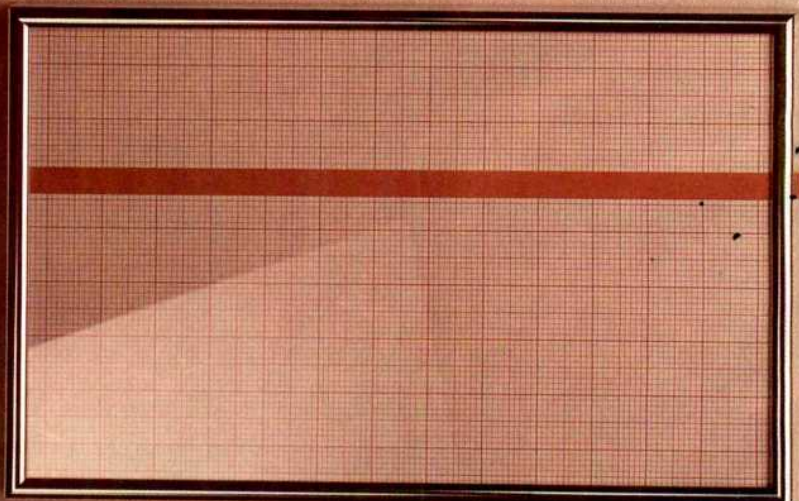
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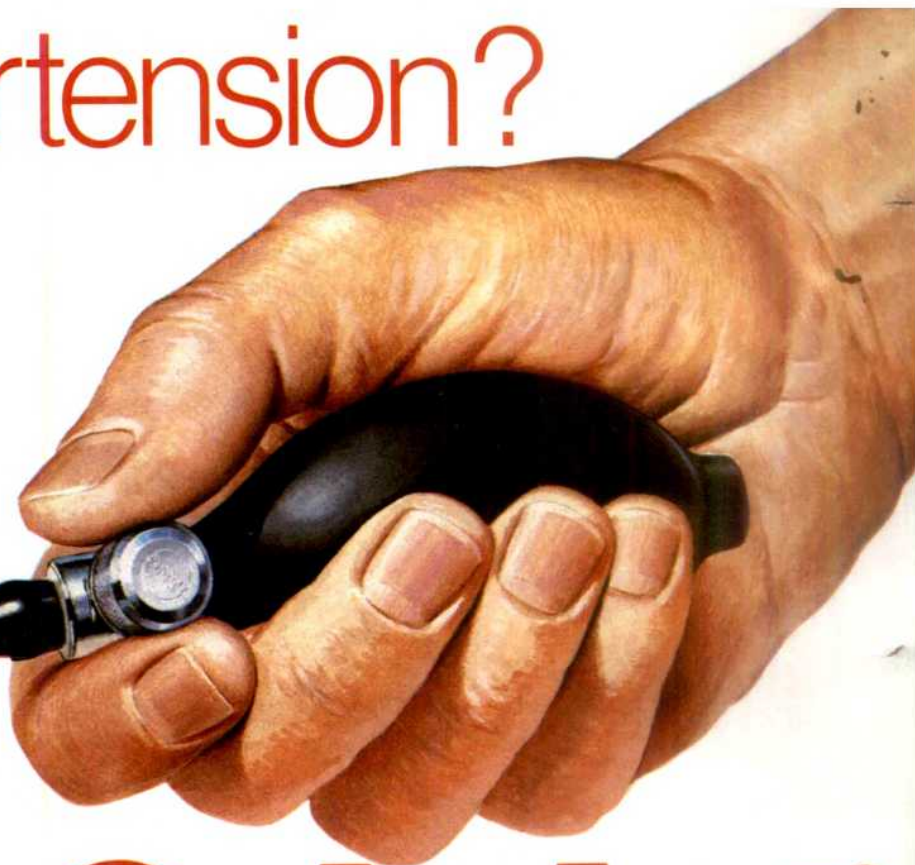
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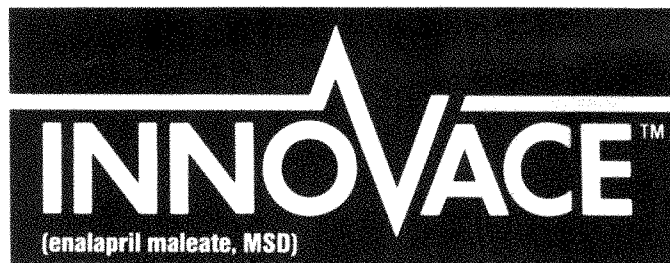
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All grades of essential hypertension.
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Essential hypertension. The usual maintenance dosage is 20 mg once daily. Treatment may be initiated with 10 mg or 20 mg once daily dependent on degree of hypertension. For mild hypertension, recommended initial dosage is 10 mg once daily. For all other grades an initial dosage of 20 mg once daily recommended.

Renovascular hypertension. Initial dose is 10 mg a day, adjusted as necessary. Most patients should respond to 20 mg daily.

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CONTRA-INDICATIONS

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Symptomatic hypotension rarely after initial dose. More likely following volume depletion caused by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Blood pressure may drop in some patients with congestive heart failure who have normal or low blood pressure.

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of 'Innovace' and their renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Some hypertensive patients, with no apparent pre-existing renal disease, have developed minor and usually transient increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required.

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PRODUCT LICENCE NUMBERS

Tablets, 5 mg, 0025/0194, Tablets, 10 mg, 0025/0195, Tablets, 20 mg, 0025/0196.

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1. Sharpe, D. N., *et al.*, *Circulation* 70, 1984, 2, 271.
2. Gomez, H. J., *et al.*, *Journal of Hypertension* (in press).
3. Kjekshus, J. K., *Scandinavian Journal of Urology and Nephrology*, 1984, Suppl. 79, p.115.



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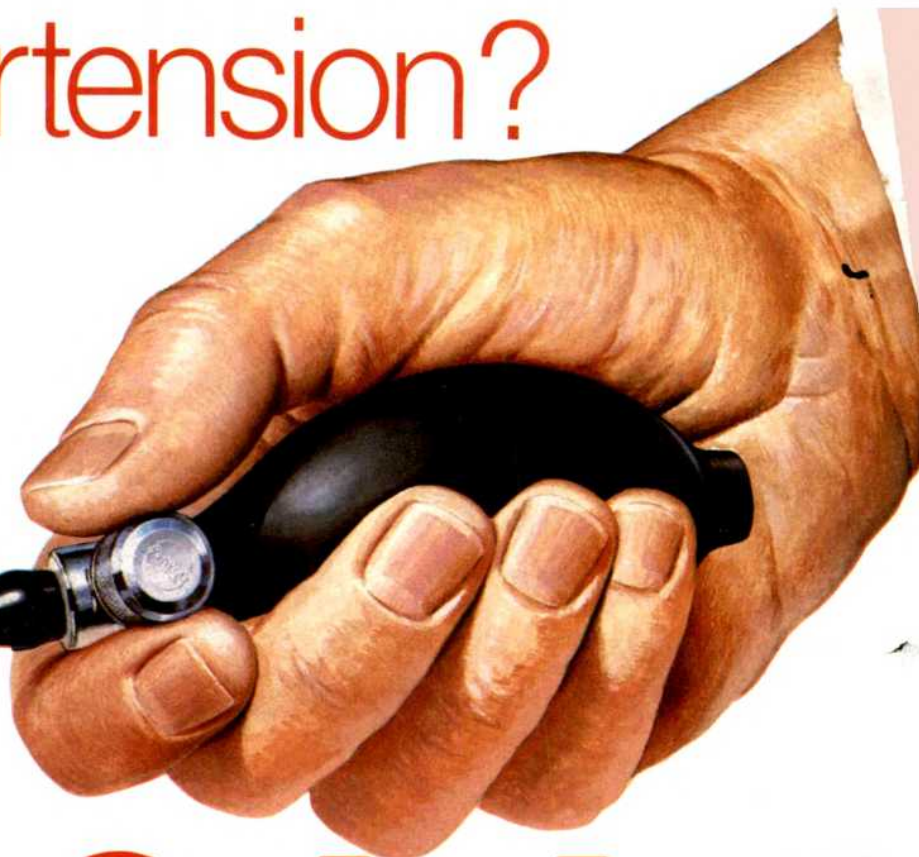
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Editorial

Strategies for preventing and screening for coronary heart disease

M F OLIVER

From the Cardiovascular Research Unit, University of Edinburgh, Edinburgh

"Strategy is simple, but not easy"—Clausewitz.

Intervention in the whole population in order to reduce the risk of coronary heart disease through altering lifestyles and specific intervention in individuals with identified high risk are complementary and not opposing strategies. Yet they are valid alternatives in that they present society with different choices and uses of its limited resources. To community health educators—and evidently to epidemiologists—mass intervention is to be preferred. To many physicians and cardiologists, the high risk strategy is likely to be more attractive. In the best of all possible worlds we should be able to afford both policies if they truly benefit society.

But, so far, the results of investment in mass intervention trials have not been impressive—with a very considerable outlay and little or no yield (see later). It is argued that such trials are unnecessary because the cost of changing lifestyle on a mass population basis is really negligible and it is not expensive to promote campaigns to tell people to stop smoking, change their diet, or take more exercise: such advice is bound to do more good than harm, it is said.

Yet improved health is not the only need of the population. Simply to argue that cigarette smoking should be eliminated without taking into account the repercussions on economy and employment is a narrow medical view. Similarly, to recommend changes in farming policy and farming economy leading to reductions in dairy farming by a quarter or a third needs much more consideration than it usually gets from the health education enthusiasts. Reduction in milk production and the requirement for less carcass fat imply a substantial reduction in animal food, of which barley is the major component.¹ Land will be released for other purposes but perhaps more than is needed for fruit and vegetables. The case for making large changes in agricultural strategy, with all its

repercussions on cereal, fruit, vegetable, and edible oil production and also on the welfare of those working in these industries, should surely be based on clear evidence that health will improve consequently. This evidence is not yet forthcoming.

Mass intervention for moderate risk

One of the underlying problems with regard to intervention to prevent coronary heart disease is the very low specificity with which we are able to identify individuals at risk. The strength of the concept relating risk factors to coronary heart disease lies in their relative or proportional risk and not in their absolute risk or predictive power. While it is undeniable that those with serum cholesterol concentrations or blood pressure in the top 10% or 20% of the population distribution have a higher risk than those with lower levels,²⁻⁴ the actual risk is low. Thus two thirds of healthy adult men, aged 40-55 years, found to have the highest risk (above the eightieth centile) as a result of raised cholesterol concentrations (excluding familial hypercholesterolaemia) and blood pressure can be estimated to remain well over the subsequent 25 years.² Hopefully, this low specificity will improve when some of the emerging measurements of thrombogenic risk have been evaluated as predictors.

It should not be a surprise, therefore, or particularly controversial, that intervention to control raised cholesterol concentrations and raised blood pressure in healthy adult men who are at moderate risk, even when conducted simultaneously and in conjunction with reduction of cigarette smoking, has not been successful on a mass basis.⁵⁻⁷ What lessons are there to learn? One argument, given in defence by enthusiasts, is that too little was done too late. We will only know if this is true when more has been done earlier. But it is impracticable to do much more: for example, attempts were made to make a profound change in the consumption of dietary fat, along the lines recommended by the World Health Organisa-

Requests for reprints to Professor M F Oliver, Cardiovascular Research Unit, Hugh Robson Building, George Square, Edinburgh EH8 9XF.

tion,⁸ in the Multiple Risk Factor Intervention Trial⁵ but it is quite clear from the disappointing reduction in plasma cholesterol concentrations (let alone the lack of change in the incidence of coronary heart disease) that compliance was bad—in spite of advice received from teams of physicians, dietitians, sociologists, and psychologists. To do more with regard to the control of blood pressure means the life time use of potent drugs with their attendant side effects. More might be done, however, with regard to cigarette smoking, although the chances of eliminating this are negligible. Another common argument from those committed to mass intervention is that five to 10 years is too short a period to appraise results of trials because coronary atherosclerosis takes many years to develop and an equal period may be necessary to prove the effectiveness of changes in lifestyle on coronary heart disease. May be, but coronary atherosclerosis and coronary heart disease do not equate, and even successful demonstration of regression of coronary atherosclerosis does not necessarily mean less coronary heart disease. There are no large randomised multiple risk factor intervention trials against coronary heart disease proceeding into a second decade of testing, and so how shall we know? Evidently, we will have to rely on being able to interpret national trends in coronary heart disease mortality rates in terms of prevention policies, but there are so many confounding influences that this does not look promising.

Selective intervention for high risk

The scientific evidence for intervention in those at high risk for coronary heart disease on account of hypercholesterolaemia is much better than for those at moderate risk. But it is still unsure because the numbers in the two main trials—the Oslo trial⁹ and the Lipid Research Clinic Coronary Primary Prevention Trial,¹⁰ in which very high (above the ninetieth percentile) serum cholesterol concentrations were reduced—are too small and the margins of difference in coronary heart disease rates too narrow for it to be certain that whether and how big a proportion of people will benefit from treatment. In the Oslo Heart Study, comprising 1232 men aged 40–49, there was a significant reduction ($p < 0.03$) in the mixed end point of cardiac death and non-fatal myocardial infarction; but there was one case of sudden death in the control group with was “unexplained” and, were this case not to be due to coronary heart disease and were it to have been randomised to the intervention group, total coronary heart disease and total cardiovascular events would not have been significant at the 5% level.¹¹ The Lipid Research Clinic Coronary Primary Prevention Trial showed a 19% fall, again in a mixed end point of

coronary deaths and non-fatal myocardial infarction, at the 4% level of significance using a one tail test of significance. While the confidence limits of +3% and +32% (or -0.1% and +3.5% considering difference in risk¹¹) surrounding the main end points do not provide a sound enough basis to argue, as the authors have done, that these results provide the basis for lowering moderately raised cholesterol and low density lipoproteins in populations less highly at risk, the consistency between the results of these two trials is impressive. Additionally, there were in the Lipid Research Clinic Coronary Primary Prevention Trial non-significant reductions in the incidence of angina, abnormal exercise electrocardiogram tests, and referrals for coronary artery surgery. There was also a reduced rate of coronary heart disease incidence in three other trials of reducing high concentrations of serum cholesterol—the World Health Organisation clofibrate trial¹² and the Helsinki Mental Hospitals¹³ and Veterans Administration Studies,¹⁴ where diets with a high ratio of polyunsaturated to saturated fats were used.

The frailty of the case is added to by the fact that all these studies, including the dietary intervention trials, showed an increase in non-cardiovascular mortality, and in several of them the order of magnitude of this increase was comparable to that of the decrease in coronary heart disease.¹⁵ The increase in non-cardiovascular mortality in the World Health Organisation clofibrate trial has recently been shown to relate closely to the period of administration of the drug,¹⁶ and the increase in the incidence of oral-gastrointestinal cancers which occurred in the Lipid Research Clinic Coronary Primary Prevention cholestyramine trial should not be dismissed as a random change in cancer prevalence, since a plausible explanation—a change in local pH due to the anion-exchange resin—may be advanced.

It has been argued¹⁷ that the results of all trials—when lumped together, regardless of treatment and regardless of design, numbers, and mixed end points—show a mathematically convincing benefit for coronary heart disease. This is, to me, too simplistic biologically: but, even if it is a valid way to appraise the results of trials, the same approach shows an adverse effect for total and non-cardiovascular mortality which cannot easily be dismissed.

The basis for intervening in those at high risk on account of severe hypertension is that the incidence of strokes is less. Were this not so, it might be hard to make a strong case for lowering moderately raised blood pressure in order to reduce coronary heart disease for the evidence of benefit is unconvincing¹⁸ and may even, in those with pre-established signs of myocardial ischaemia, be harmful.⁵

Nevertheless, I think that the case for intervention

in individuals at very high risk for coronary heart disease is greater than the case for doing nothing and that we are justified in exposing them to the risks of drugs and inconvenience of stringent dietary changes. The American Heart Association has recently made appropriate recommendations for the management of such people.¹⁹ How may we best identify such individuals?

To screen or not to screen

Just as there are alternative conceptual approaches to intervention, there are alternatives for screening the population in order to identify people most at risk for coronary heart disease.

Screening is irrelevant to those who propound a policy of mass prevention since they wish to advise the whole population to change its lifestyle now. But for those who have doubts about the value and practicability of mass intervention and who endorse the high risk strategy the difficult question of how to screen the population simply, cheaply, effectively, and without producing anxiety must be addressed.

The alternatives are to screen the male adult population or to try to identify, mostly through clinical expertise, those at maximum risk (case finding). Our individual and collective approach to these will depend to an extent on that part of medicine we represent—community care doctors or practising physicians and cardiologists.

The best policy would, at present, seem to be that we should aim at identifying those above the eightieth percentile of the distribution of serum cholesterol concentrations or blood pressure for that population for which it is planned to give advice (this is not necessarily the same numerical cut off point for all populations). There are three reasons for adopting this attitude. One is that the relation of a given risk factor to the subsequent development of coronary heart disease is increasingly diluted by other known and unknown factors at lower deciles—in other words, specificity decreases. It is relatively good at high levels: recent figures for the Multiple Risk Factor Intervention Trial indicate that nearly 50% of cases of coronary heart disease “attributable” to high serum cholesterol concentrations occur in those with serum concentrations above the eightieth percentile, and 30% of cases occurred in those above the ninetieth percentile²⁰; and the United Kingdom/World Health Organisation trial has also shown, taking four factors into account, that 32% of “attributable” cases occur in those above the eighty fifth percentile of risk.²¹ A second reason is that successful treatment of very high concentrations of serum cholesterol and of blood pressure require the use of drugs; and these should be acceptable ethically to physicians and cardiologists

only when the risk of the disease is at least equal to the risk of giving drugs²² and to symptomless people when there is a really valid reason for making big changes in their lifestyle and committing them to drugs for the rest of their days. A third reason for a high cut off point is that the ratio of cost to benefit increases when intervention is attempted below the eightieth percentile owing to greater use and therefore costs of drugs in relation to a decreasing amount of ultimate benefit to be expected.

Screening of all male adults

Two considerations at least need to be thought through by those who advocate screening of the adult male population for subsequent implementation of high risk intervention against coronary heart disease. One is the practicability, costs, and advantages to society of universal screening and the other is possible disadvantages and the advice to be given to those for whom specific intervention is not really indicated. Incidentally, data concerning the relation of risk factors to coronary heart disease in women are far less well assembled than for men, and none of the clinical trials referred to above have included women: the probability is that the prevalence of risk factors is lower and that their significance is less and, until more formal evidence is available, a case for screening the adult female population cannot be adequately established. Additionally, most of the data relating risk factors to coronary heart disease have come from studies of the under 60 age groups and there is really no case for screening—and expecting subsequent benefit—in those over 60: the emphasis should be on the young and middle aged.

While a blood pressure measurement is easy and acceptable to most, a venepuncture is less so; special facilities and improved laboratory services might need to be established in some areas. There are about 12.5 million men aged 15–55 in the United Kingdom. The cost of estimating serum cholesterol concentrations is in the region of £3, or £37.5 million for this population.

In order to focus on the top 20% at highest risk, a repeat estimate would be necessary together with measurement of high density lipoprotein (HDL) cholesterol (at about £3), and this might add £15 million to the sum. Thus, identification of the top quintile might cost £50 million or more, but this calculation is for biochemical analyses and not for staff and facilities necessary to do venepunctures. Such expenditure might allow 2.5 million men to receive treatment to lower their very high serum cholesterol. Extrapolating from the Lipid Research Clinic Coronary Primary Prevention Trial results,¹⁰ coronary heart disease might be postponed or prevented in

about 70 000 men over a seven year period. It is for health economists and politicians to decide if this a worthwhile yield. But there are still other problems.

Screening of the adult male population will identify many with raised cholesterol concentrations and raised blood pressure between the fiftieth and eightieth percentile. What should we tell these people? We know that their risk of coronary heart disease is only slightly increased above that for those in the three deciles below the median, we know that prediction of coronary heart disease is weak and that it cannot be individualised, and we know that mass intervention has so far been singularly disappointing. Even in a health conscious community, I cannot believe that informing these men about their serum cholesterol concentration or blood pressure will be conducive to reassurance so long as the medical profession lacks a strong base for advice or action. Indeed, it is likely to increase anxiety in many. Physicians and cardiologists who support male adult population screening programmes should, therefore, first ask themselves what they will advise when screening identifies an otherwise fit, non-obese, 35 year old man with serum cholesterol concentration or blood pressure in the sixth or eighth deciles. Should he be told? If so, what should he be told about his individual risk and how to reduce it? Should the test be repeated in one or five years time, or should the mildly abnormal result be completely ignored? Each of these questions needs to be identified and answered by policy makers.

Selective screening

There are problems of comparable difficulty for those who advocate selective screening on the basis of clinical acumen, or case finding. The biggest of these—and there is no information available at present—is the proportion of high risk individuals (above the eightieth percentile) that would be missed by even the most assiduous programmes of clinical screening. Were this to be large, then the strategy of selective screening would probably have to be abandoned in favour of mass screening.

Selective screening may identify currently symptomless individuals with pronounced hypercholesterolaemia; it is less suitable for finding those with severe hypertension, except through hypertensive families. The finding of tendon xanthomata, for which a routine search should be made, points to monogenic familial hypercholesterolaemia, but this only comprises about 15% of those with severe hypercholesterolaemia with most being polygenic. Identification of a premature corneal arcus or xanthelasma should spread the net a little wider, and it is interesting that opticians do not seem to look for these features routinely. The recent American Heart

Association recommendations¹⁹ emphasise that family screening can be the key to diagnosis and a big yield might come from the first degree relations of all patients who have developed any clinical features of coronary heart disease under the age of about 50.²³ In my experience, it is rare for physicians and cardiologists in hospitals dealing with large numbers of coronary heart disease patients to screen first degree relations routinely for raised serum cholesterol concentrations and blood pressure. This is a matter of improving education since family doctors especially should be able to add considerably to the yield by identifying families with aggregation of vascular disease and screening the apparently healthy relatives.

One advantage of case finding is that the motivation of patients to identify their high risk relatives and of their doctors to intervene will be far higher than that for the general population. It is now up to physicians and cardiologists to join with epidemiologists and demonstrate from population surveys whether or not the majority of those at high risk are identified by selective screening on the basis of case finding.

Improvement of prediction

Whichever screening strategy is favoured, there will be many who will develop coronary heart disease in whom it was not predicted or predictable. The strengths and weaknesses of the classical risk factors of cigarette smoking, raised cholesterol concentration, and raised blood pressure in predicting coronary heart disease are now well established, and little new in terms of measurements for screening the population for coronary heart disease has become available during the past 10 years.

Sharpening of the methods for identifying those at very high risk is overdue. Perhaps the most obvious and urgent area is prediction of incipient thrombogenesis. Identification of new deoxyribonucleic acid polymorphisms—such as, for example, atherogenic apoprotein gene clusters—which might be applicable to some readily available tissue, like skin, is one hope. Knowledge of the factors that make people intrinsically resistant to coronary heart disease is another, and more studies are needed of the characteristics of families and people who do not get coronary heart disease: it is an area of almost complete ignorance.

One of the greatest priorities, then, for the control of coronary heart disease is to improve both the sensitivity and the specificity with which we are able to predict its development. When this has been achieved the case for screening will be strengthened.

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Myocardial infarction and thrombolysis

Electrocardiographic short term and long term results using precordial mapping

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SUMMARY In a consecutive series of 56 patients with acute myocardial infarction, ST segment depression and elevation in the electrocardiographic limb leads I, II, and III were summated for each patient before and immediately after intracoronary streptokinase infusion and the results compared with the angiographic findings. Forty three patients had angiographically confirmed reperfusion of an initially occluded vessel and showed a significant decrease in summated ST shift. The ST segment changes in the limb leads virtually returned to normal in all 43 patients, and in most, inverted T waves developed. Thrombolysis was unsuccessful in 10 patients, and the infarct related coronary artery was already patent in three. When these two groups are combined, all 13 patients without reperfusion showed no significant change in summated ST segment shift. During percutaneous transluminal angioplasty inflation of the balloon in the vessel that was previously occluded simulated reocclusion and was followed by new ST elevation if the artery supplied viable myocardium.

In a further consecutive study of 54 patients with anterior myocardial infarction, the precordial R waves and Q waves were studied over the four to six months following infarction using a standardised 48 electrode mapping system. All patients underwent a repeat angiogram after four to six months. In 36 patients the infarct related vessel was patent. They showed a significant mean increase in summated precordial R wave amplitude and a reduction in the mean number of precordial leads without R waves. In 18 patients with unsuccessful thrombolysis or reocclusion there was a further reduction in mean summated R wave amplitude and an increased number of precordial leads not showing R waves.

Precordial R wave mapping seems to be a valuable non-invasive method of assessing the salvage of myocardium after reperfusion and the damage caused by reocclusion. Loss of R waves in the acute phase of myocardial infarction does not necessarily mean an irreversibly damaged myocardium.

Electrocardiography is the most important technique for diagnosing acute myocardial infarction. ST segment elevation occurs within a few seconds of complete occlusion of a coronary artery. During the next six to eight hours R waves are lost or their amplitude reduced and pathological Q waves develop.^{1,2}

A rapid decrease in ST elevation during intravenous streptokinase infusion in patients with acute myocardial infarction was described in the 1960s,³

and changes in the standard electrocardiographic leads after intracoronary streptokinase infusion have recently been reported.^{4,5} There are, however, no detailed studies that have used electrocardiographic mapping to study the effectiveness of reperfusion. We therefore studied the ST segment changes during angiographically documented reperfusion and the Q and R wave changes in the subacute and chronic stages of myocardial infarction.

Patients and methods

The patients in the present study were all admitted to our hospital within eight hours of the onset of chest pain, had electrocardiographic changes consistent

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Accepted for publication 5 March 1985

with acute myocardial infarction (ST elevation of ≥ 0.2 mV in the limb leads or of ≥ 0.3 mV in the chest leads), and had persistent chest pain. They were treated with an intracoronary infusion of streptokinase at a dose of 3000 units per minute for 60 minutes. Coronary angiography was performed before, every 20 minutes during, and at the end of the infusion.

The protocol was approved by the local ethical committee, and all patients gave informed consent for the study.

ST SEGMENT CHANGES IN THE ACUTE STAGE (Group 1)

In a consecutive series of 56 patients (group 1) (47 male, nine female; age range 41–81 years) 21 had anterior and 35 inferior infarcts. We summated the ST segment elevation and depression (ST shift) in the limb leads I, II, and III before and after streptokinase infusion and compared the results with the angiographic findings. In 34 patients online monitoring of the ST segment using up to eight precordial leads was performed during the 48 hours after streptokinase infusion in order to detect recurrent ischaemia.⁶ In six patients we used a precordial online mapping system to study the ST segment changes during balloon inflation while performing percutaneous transluminal angioplasty of the remaining stenosis of an infarct related vessel after successful reperfusion.

CHANGES IN Q AND R WAVES AT SIX MONTHS (Group 2)

In a second series of 54 consecutive patients (group 2) with anterior myocardial infarction (41 male, 13 female; age range 27–79 years), which did not include the patients in group 1, standardised 48 electrode precordial mapping was performed immediately after streptokinase infusion, at 72 hours, at three weeks, and at four to six months, when repeat coronary angiography was also performed.

The 54 patients in group 2 were divided into four groups according to the angiographic findings at follow up coronary angiography four to six months after

infarction. Group A comprised 11 patients in whom reperfusion occurred spontaneously before streptokinase infusion and the infarct related vessel was patent four to six months later; group B comprised 25 patients achieving successful thrombolysis in whom the infarct related vessel was still patent four to six months later; group C comprised eight patients with reoccluded vessels at four to six months; and group D comprised 10 patients in whom thrombolysis was unsuccessful.

STATISTICAL ANALYSIS

Statistical analyses were performed using Student's *t* test. Values are expressed as mean (standard deviation).

Results

GROUP 1

In 43 of the 56 patients the infarct related vessel was occluded at the start of the streptokinase infusion, thrombolysis was successful, and reperfusion was achieved. In these patients there was a significant decrease in mean summated ST shift from $0.68(0.32)$ mV to $0.09(0.12)$ mV ($p < 0.001$). Figure 1 shows an example of an electrocardiogram that had virtually returned to normal a few minutes after reperfusion.

In 10 patients either the occluded vessel could not be reperfused or inadequate reperfusion was achieved. In three patients the vessel was already patent before the start of the streptokinase infusion. In this combined group of 13 patients there was no significant change in mean ST shift during streptokinase infusion (mean ST shift before infusion $0.44(0.29)$ mV and after infusion $0.44(0.36)$ mV) (Fig. 2). All patients achieving successful reperfusion showed a reduction in mean ST shift of $> 55\%$ within one hour.

During percutaneous transluminal coronary angioplasty performed three days after successful thrombolysis in four of these six patients inflation of the

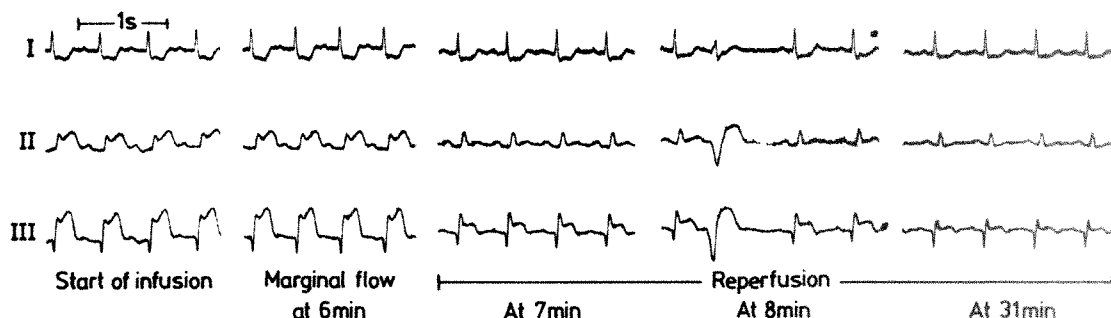


Fig. 1 Electrocardiograms showing rapid "improvement" of ST-T changes after reperfusion in a 45 year old man in whom a streptokinase infusion into the occluded right coronary artery was started four and a half hours after the onset of chest pain.

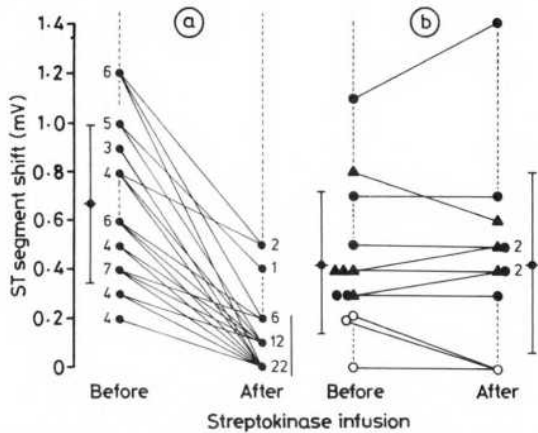


Fig. 2 ST segment shift in leads I, II, and III before and one hour after streptokinase infusion in (a) 43 patients with successful thrombolysis and reperfusion and (b) 10 patients with unsuccessful thrombolysis (● inferior, ▲ anterior infarction) and three with the infarct related vessel already patent at the start of infusion (○). Bars represent mean (SD).

balloon in the remaining stenosis of the infarct related vessel simulated reocclusion and was accompanied by new elevation of the ST segment in the precordial

leads around the centre of the initial ischaemia (Fig. 3). In two patients no ST segment changes were seen during angioplasty. Although initial reperfusion had been successful and both patients had shown a reduction in mean ST shift during the first hour, they had both had subsequent episodes of recurrent chest pain and ST elevation, repeated estimations of plasma creatine kinase MB activity had shown a delayed release pattern, and left ventricular angiography showed severely depressed regional wall motion.

GROUP 2

Groups A and B showed a moderate but significant increase in precordial R wave amplitude between the initial admission and repeat angiography, whereas patients in groups C and D showed a further loss of amplitude (Table). A similar trend could be seen with respect to the number of precordial leads showing a complete loss of R waves: in groups A and B the number of leads decreased, but increased or remained the same in groups C and D. Four to six months after infarction group A had the fewest precordial leads with complete loss of R waves (mean 12.3) and group C the most (mean 31) (Table). The increase in R wave amplitude in groups A and B could

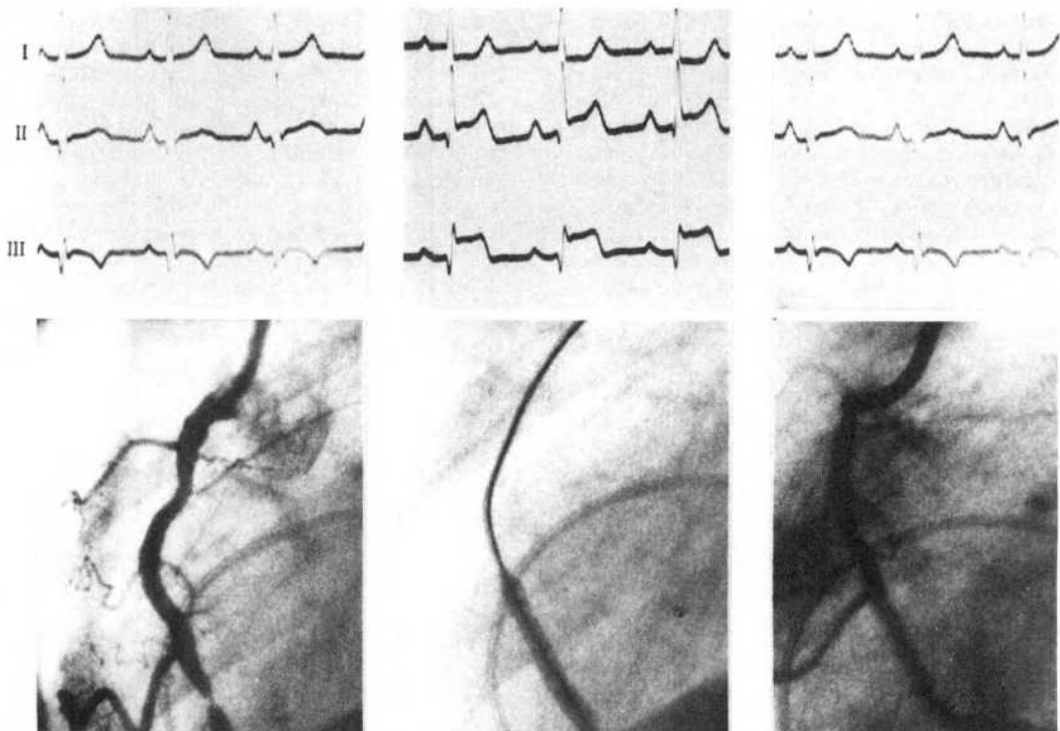


Fig. 3 Electrocardiograms and angiograms showing simulation of reocclusion during inflation of the balloon causing new ST elevation in leads II and III in a patient with inferior myocardial infarction and successful thrombolysis two days previously.

Table Mean (SD) of summated R wave amplitude (mV) and mean (SD) number of leads showing no R waves in a 48 electrode precordial map recorded immediately after intracoronary streptokinase infusion and 4–6 months later in group 2 patients with an initially patent infarct related vessel (group A), successful thrombolysis with vessel remaining patent (group B), unsuccessful thrombolysis (group D), and successful thrombolysis with subsequent reocclusion (group C)

Subgroup	No of patients	Summated R wave amplitude (mV)				Mean (SD) No of leads showing no R waves			
		After infusion	After 4–6 mth	Change	p value	After infusion	After 4–6 mth	Change	p value
A	11	18.1 (5.4)	23.2 (7.0)	+5.1 (7.5)	<0.04	14.7 (10.8)	12.3 (7.5)	-2.4 (4.8)	NS
B	25	12.4 (10.9)	16.2 (11.2)	+3.9 (5.0)	<0.006	27.9 (13.1)	21.2 (13.7)	-6.6 (8.9)	<0.001
C	8	14.0 (13.0)	9.8 (11.0)	-4.3 (2.8)	<0.003	26.5 (12.2)	31.0 (12.2)	+4.3 (3.2)	<0.007
D	10	11.8 (12.8)	10.7 (12.7)	-1.1 (4.8)	NS	30.4 (12.2)	30.7 (12.6)	+0.3 (10.7)	NS

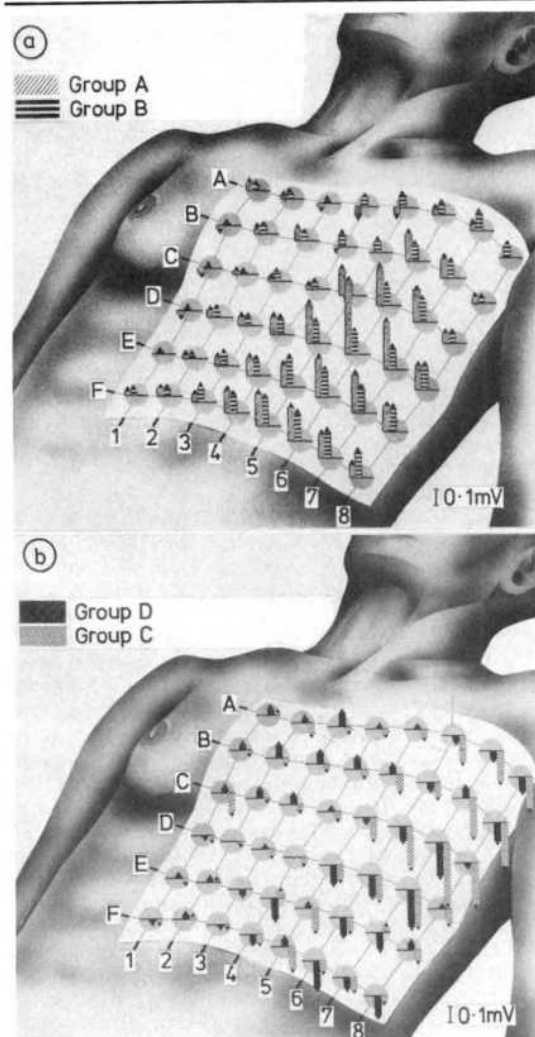


Fig. 4 Diagrams showing (a) increase in R wave amplitude (related to position of electrode and mean value in each of the four groups) during the 4–6 months after infarction in patients with initially patent infarct related vessel (group A) and those with successful thrombolysis in whom the vessel remained patent (group B) and (b) decrease in R wave amplitude in patients with unsuccessful thrombolysis (group D) and those with reocclusion of the infarct related vessel (group C).

be seen in those electrodes having the highest ST segment elevation at the time of admission, whereas in patients with reocclusion (group C) the further loss of R wave amplitude mainly affected the border zone of initial precordial ischaemia (Fig. 4b).

Discussion

In this study a decrease in ST elevation and ST depression in the electrocardiographic limb leads occurred within one hour after reperfusion of the infarct related vessel in patients with anterior or inferior myocardial infarction treated with intracoronary streptokinase. In patients with unsuccessful thrombolysis no change in summated ST shift occurred during streptokinase infusion. Similar results have been reported in patients with anterior myocardial infarction using leads V1–V6.^{4,5,7} This rapid reduction in summated ST depression coincides with the relief of pain. Although it might be explained by rapid death of the infarct area, a reduction in ischaemia is more likely since reocclusion or simulated reocclusion by balloon inflation at the same site induced a new ST elevation (Fig. 3).

This simple electrocardiographic criterion should be useful for judging the likelihood and timing of reperfusion in patients treated with intravenous streptokinase.

It is generally accepted that the loss of R waves and the appearance of new Q waves after acute myocardial infarction represent loss of myocardium.^{8–11} The time course of these changes has been investigated in detail during the first 48 hours after the onset of chest pain.^{2,10} During this period a recovery of R waves and a regression of Q waves was found in <10% of conservatively treated patients.² Although transient Q waves have been reported in patients with Prinzmetal's angina, during myocardial ischaemia or coronary arteriography, or after coronary artery bypass surgery,^{12–16} they are rare after myocardial infarction and are confined to patients with small infarcts.^{17,18} The mechanism is unknown; some authors believe that shrinking of the scar and hypertrophy of the myocytes in the border zones is the most likely reason.^{18,19}

In this study patients with unsuccessful throm-

bolysis (group D) had no significant change in precordial Q waves or R waves when the acute and chronic stages are compared, whereas an extension of the electrocardiographic infarct area was seen in those with angiographically documented reocclusion (group C). Although the numbers of Q waves and the precordial R wave amplitudes immediately after streptokinase infusion were nearly the same in groups B and C, patients in whom reperfusion was maintained showed a gradual but significant reduction in the number of Q waves and an increase in R wave amplitude in the centre of the infarct during the weeks after reperfusion. Patients with spontaneous reperfusion (group A) had the smallest infarct areas and no significant change in Q waves during long term follow up. Thus shrinking of the scar and hypertrophy of the healthy myocardium cannot be the only explanation for the increase in R wave amplitude. The significant increase in R wave amplitude and the reduction in the number of pathological Q waves after reperfusion probably means salvage of jeopardised myocardium. Obviously, the electrical recovery of the ischaemic cell takes more than a few days and coincides with the recovery of function.²⁰

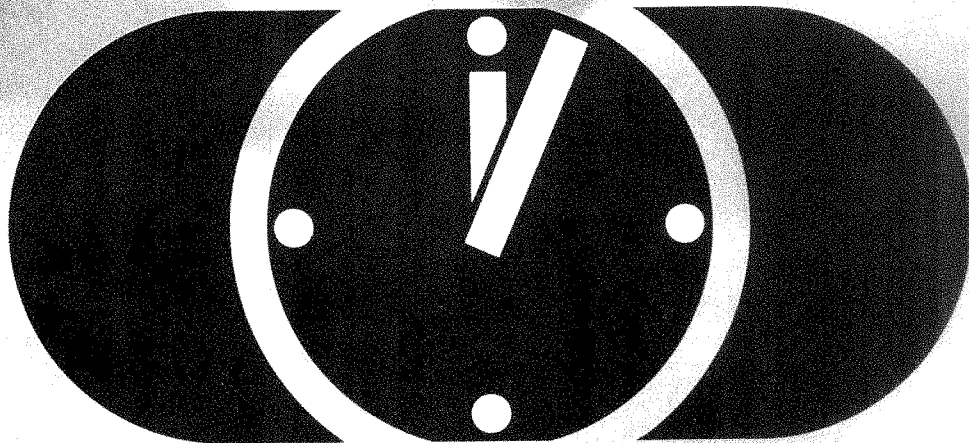
Since there is a significant difference in these electrocardiographic findings between patients in whom the infarct related vessel could be reperfused within the first four to six hours and those in whom reperfusion was unsuccessful, precordial mapping should be a useful non-invasive method for judging the long term effects of reperfusion. These results will need to be confirmed in a prospective randomised study.

This study was undertaken with the support of Deutsche Forschungsgemeinschaft SFB109.

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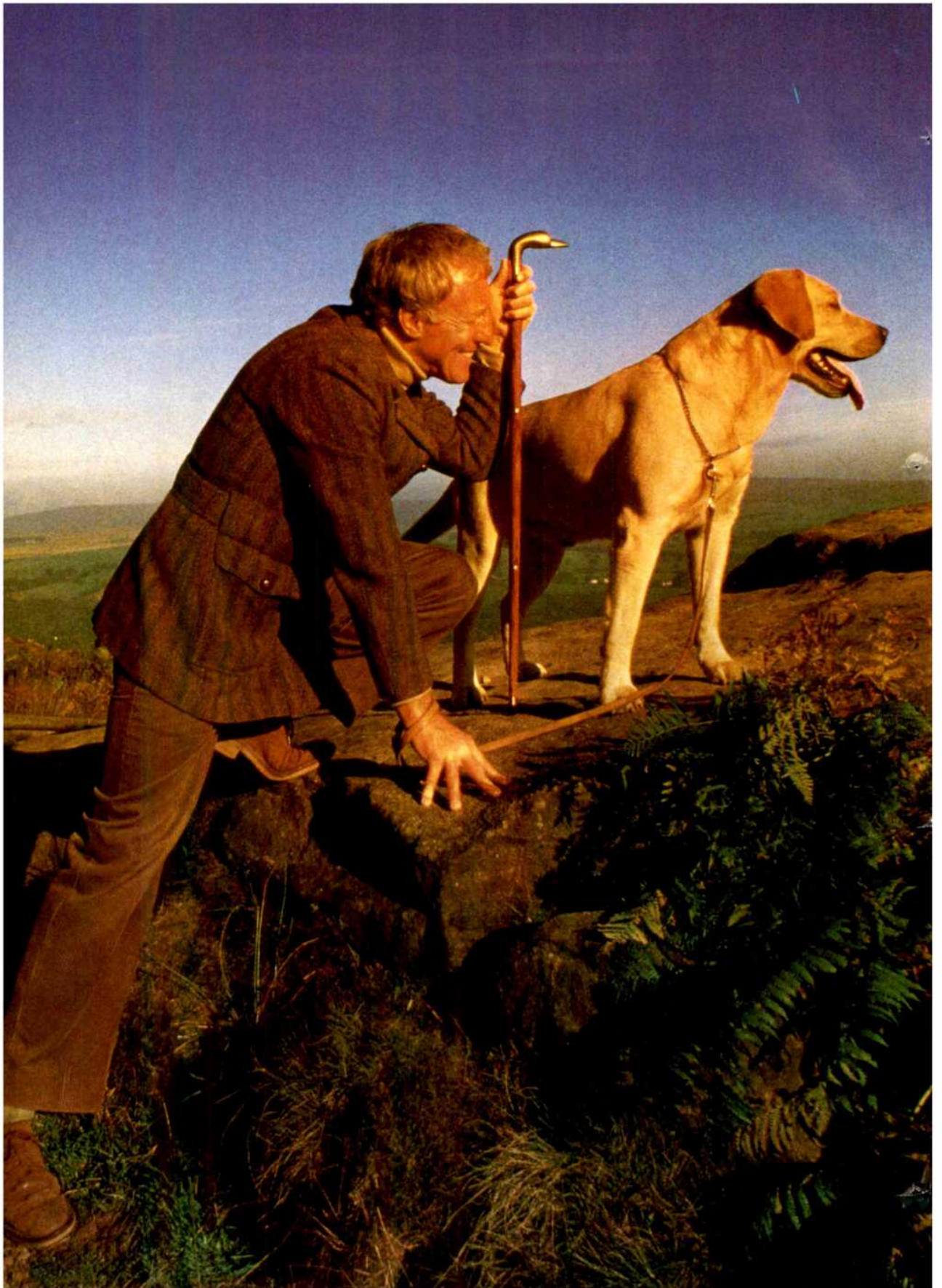
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'Inderal' LA, Half-'Inderal' LA: abridged prescribing information. Dosage Angina, anxiety, essential tremor, thyrotoxicosis, prophylaxis of migraine: 1 capsule Half-'Inderal' LA, once daily, increased, if necessary, to 1 capsule 'Inderal' LA, once daily and a further increment of Half-'Inderal' LA. Hypertension: 1 capsule 'Inderal' LA, once daily, increased, as necessary, in increments of Half-'Inderal' LA. (In appropriate patients e.g. the elderly, starting dose is 1 capsule of Half-'Inderal' LA, once daily). **Contraindications** Heart block, Bronchospasm, Prolonged fasting, Metabolic acidosis. **Precautions** Untreated cardiac failure, Bradycardia, Modification of tachycardia of hypoglycaemia. Transference from, or discontinuance of, clonidine. Prescription of Class 1 antiarrhythmic agents. Co-administration with verapamil. Anaesthesia. **Pregnancy. Adverse Reactions** Cold extremities, nausea, insomnia, lassitude and diarrhoea are usually transient. Isolated cases of paraesthesia of the hands, rashes and dry eyes have been reported with beta-blockers. Consider discontinuance if they occur. Beta-blockers should be withdrawn gradually. **Overdosage** See data sheet. **Basic NHS cost** 28-day calendar pack, 'Inderal' LA £6.66, Half-'Inderal' LA £4.48 PL Nos. 'Inderal' LA 29/0128, Half-'Inderal' LA 29/0173 *Trademark. 'Inderal' is a trademark for propranolol hydrochloride B.P.

'Inderex': abridged prescribing information. Dosage One capsule daily in hypertension. **Contraindications** Heart block, Bronchospasm, Anuria, renal failure or thiazide sensitivity. Prolonged fasting. Metabolic acidosis. **Precautions** Untreated cardiac failure, Bradycardia. Modification of tachycardia of hypoglycaemia. Transference from, or discontinuance of, clonidine. Prescription of Class 1 antiarrhythmic agents. Co-administration with verapamil. Diabetes. Digitalis-containing preparations. Hepatic cirrhosis with ascites. Co-administration of lithium-containing preparations. Anaesthesia. **Pregnancy. Adverse Reactions. Propranolol Hydrochloride** Cold extremities, nausea, insomnia, lassitude and diarrhoea are usually transient. Isolated cases of paraesthesia of the hands, rashes and dry eyes have been reported with beta-blockers. Consider discontinuance if they occur. Cessation of beta-blocker therapy should be gradual. **Bendrofluazide** Hypokalaemia. Hyperuricaemia. Rare reports of rashes, necrotising vasculitis, acute pancreatitis blood dyscrasias and aggravation of pre-existing myopia. **Overdosage** See data sheet. **Basic NHS cost** 28-day calendar pack £7.44 PL No. 29/0157 'Inderex' is a trademark for propranolol hydrochloride B.P. in a long acting formulation and bendrofluazide B.P.



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and **MONO-CEDOCARD 40**
(isosorbide mononitrate)

for patients who require increased dose therapy

PRESCRIBING INFORMATION

Presentation: Round white tablets, embossed "Mono CC" (Mono-Cedocard 20) or "40 Mono 40" (Mono-Cedocard 40) on one side, reverse side scored, containing 20mg or 40mg isosorbide 5-mononitrate.

Uses: For the prophylaxis of angina pectoris. Isosorbide mononitrate, the active constituent of Mono-Cedocard, is the major active metabolite of isosorbide dinitrate. It has significant vasodilator activity, the strongest effect being exerted on the venous system, and a lesser effect on the arterial circulation. As a consequence, the heart has less work to perform against diminished resistance, and therefore oxygen requirement is reduced. After oral administration, isosorbide mononitrate is well absorbed, a haemodynamic effect being measurable within 15-20 minutes. In contrast to isosorbide dinitrate, the mononitrate is not subject to first-pass metabolism.

Dosage and Administration: For oral administration.

Adult dose: Mono-Cedocard 20 — one or two tablets to be taken two or three times daily. Mono-Cedocard 40 — one tablet twice a day taken after meals.

The tablets should be swallowed (without chewing) with a little water.

Dosage for the Elderly: The dosage of nitrates in cardiovascular disease is usually determined by patient response and stabilisation. Clinical experience has not necessitated alternative advice for use in elderly patients.

There is no dose recommendation for children.

Contra-indications, Warnings, etc.

Contra-indications: In acute myocardial infarction with low filling pressures. In acute circulatory failure (shock, vascular collapse). When blood pressure is very low. During the first three months of pregnancy.

Warnings/Precautions: Consumption of alcohol should be avoided during treatment, as reaction patterns may be enhanced, and the vasodilator activity of isosorbide mononitrate may be enhanced.

Adverse effects: Generally, no serious effects are to be expected. Headache, dizziness, fatigue, palpitations, orthostatic hypotension and flushing may occur, especially at the beginning of treatment. These reactions can usually be controlled by a temporary dosage reduction.

Treatment of overdose: Gastric lavage, passive exercise of the extremities of the recumbent patient will promote venous return.

Pharmaceutical Precautions:

Storage: Protect from heat and moisture.

Legal Category:

Mono-Cedocard 20: POM

Mono-Cedocard 40: P

Package Quantities:

Mono-Cedocard 20: 100 tablets

Mono-Cedocard 40: 60 tablets

Further Information:

The plasma half-life of isosorbide mononitrate is 4.2 hours.

Product Licence Number

Mono-Cedocard 20: PL 0424/0040

Mono-Cedocard 40: PL 0424/0054

Basic NHS Cost

Mono-Cedocard 20: £8.77 per 100 tablets

Mono-Cedocard 40: £8.90 per 60 tablets

Further information available from:



London, Bedfordshire, SG16 6NS

Rupture of the myocardium *Occurrence and risk factors*

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SUMMARY The occurrence of myocardial rupture was studied in a well defined unselected population of patients with acute myocardial infarction, and the group of patients who died of rupture of the heart were compared with two control groups. Of a total of 3960 patients, 1746 (44%) fulfilled the diagnostic criteria for acute myocardial infarction. Rupture was defined solely on the basis of the presence of a pathological passage through part of the myocardium, either the free wall of the left ventricle or the septum, found at necropsy or during operation. Two controls were selected for each patient and matched for age and sex, one (control group A) with acute myocardial infarction having died in hospital but not of rupture (non-rupture cardiac death) and one (control group B) with acute myocardial infarction having survived the hospital stay. Necropsy was performed in 75% of all fatal cases with acute myocardial infarction. The total hospital mortality was 19%, the highest mortality being among women over 70 years (29%). Ruptures ($n=56$) were found in 17% of the hospital deaths, or 3.2% of all cases of acute myocardial infarction. Women aged <70 had the highest incidence of rupture, 42% of deaths being due to rupture. The mean age for patients with rupture and controls was 70.5 years. The median time after admission to death was approximately 50 hours for patients and control group A. Thirty per cent of the patients with rupture occurred within 24 hours of the initial symptoms occurring. Angina and previous acute myocardial infarction were more common among control group A. Patients with rupture and control group B were mostly relatively free of previous cardiovascular or other diseases (chronic angina pectoris (>2 months) and previous myocardial infarction). Sustained hypertension during admission to the coronary care unit was more common in patients than in control group A. Hypotension and shock were more common among control group A. Most (79%) of the patients who subsequently ruptured did not receive any corticosteroids at all during the hospital stay. Severe heart failure and antiarrhythmic treatment were more uncommon among patients than among control group A. Patients with rupture received analgesics approximately three times a day throughout their stay. Control group B received analgesics mostly during the first 24 hours.

Thus female patients, patients with first infarcts, and patients with sustained chest pain should be investigated for the possibility of rupture. As many as one third (32%) of ruptures may be subacute, and therefore time is available for diagnosis and surgery.

Rupture of the myocardium after acute myocardial infarction is at present the second most important cause of death after pump failure during hospital admission.¹ Rupture may involve the interventricular

septum, the papillary muscles, or the free wall, the last site being by far the most common. Previous studies have indicated that increasing age and female sex are important risk factors but have yielded conflicting results regarding the importance of hypertension, steroid medication, prehospital morbidity, and time and frequency of rupture.²⁻⁹ Most studies lack adequate controls, are based on necropsy findings, or represent highly selected patient groups;

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Accepted for publication 11 March 1985

most are now out of date.

We studied a well defined unselected population of patients with acute myocardial infarction in order to estimate the frequency of rupture and identify the group of patients who die of rupture of the heart. We also compared them with matched controls in order to define groups of patients at increased risk of myocardial rupture.

Patients and methods

A series of consecutive patients admitted to the coronary care unit of this hospital with symptoms occurring within the previous 48 hours and suggesting acute myocardial infarction was studied. The hospital serves a geographically and demographically well defined area with a population of 260 000, from which all cases of suspected acute myocardial infarction are admitted without any preselection regarding age, previous disease, or clinical condition. After admission all patients routinely remain in the unit until they have been without chest pain or arrhythmias for 48 hours. Patients are kept in bed for the initial 24 hours and then mobilised.

From 1 January 1979 to 31 December 1982 a total of 3960 patients were admitted to the unit. Of these, 1746 (44%) fulfilled a diagnosis of acute myocardial infarction based on two of the following criteria: clinical history, typically increased enzyme activity above the normal value, and typical evolution of the electrocardiogram.

DEFINITIONS

Myocardial rupture was defined solely on the basis of the presence of a pathological passage through part of the myocardium, either the free wall of the left ventricle or the septum, found at necropsy or during operation. Thus patients who died with a clinical picture suggesting rupture but who were not examined at necropsy were not included. Five patients with isolated rupture of the papillary muscles were also excluded.

Clinical history

Angina—The presence of angina was based on a history of angina on exertion as stated by the patient on admission to the hospital. Patients with angina for less than two months were studied separately.

Previous myocardial infarction—This was defined as a previous admission to hospital with a diagnosis of acute myocardial infarction according to the above criteria.

Hypertension was defined as a history of treatment with antihypertensive drugs because of high blood pressure.

Sustained hypotension was defined as a systolic blood pressure of ≤ 90 mm Hg on more than two occasions. Hypotension due to any obvious cause (arrhythmia, drug side effect) was excluded as was hypotension occurring during the final two hours before death. Since blood pressure was routinely recorded four times an hour at most hypotension had to be present for at least 30 minutes.

Shock was defined as hypotension (according to definition above) occurring in combination with signs of poor peripheral circulation (coldness, pallor), or oliguria, or mental confusion or all three.

Sustained hypertension was defined as a systolic blood pressure of ≥ 170 mm Hg or diastolic pressure of > 105 mm Hg on more than two occasions during the entire hospital stay. Since blood pressure was routinely recorded four times an hour at most hypertension had to be present for at least 30 minutes.

Heart failure was defined as the presence of basal pulmonary rales or dyspnoea requiring treatment with oral diuretics or intravenous injections of diuretics or increased doses of diuretics in patients already treated with diuretics on admission. Modest heart failure was defined as failure requiring oral or intravenous diuretic treatment (or increased doses) or both twice a day at most. Severe heart failure was defined as that requiring intravenous injections of diuretics three or more times a day.

Inpatient corticosteroid treatment consisted of a single administration of prednisolone (5–10 mg orally) in patients with persistent chest pain of suspected

Table 1 Distribution of myocardial infarcts and ruptures by age (years) and sex

	Total No (%) of patients with AMI	Total No (%) of deaths	Myocardial rupture		
			No	% Of AMI	% Of deaths
Men:					
<70	815 (46)	105 (13)	15	1.8	14
≥70	439 (25)	112 (26)	13	2.9	12
All	1254 (72)	217 (17)	28	2.2	13
Women:					
<70	215 (12)	31 (14)	13	6.0	42
≥70	277 (16)	81 (29)	15	5.4	19
All	489 (28)	112 (23)	28	5.7	25
Men and women (all ages)	1746 100	329 (19)	56	3.2	17

*Of patients with acute myocardial infarction (AMI).

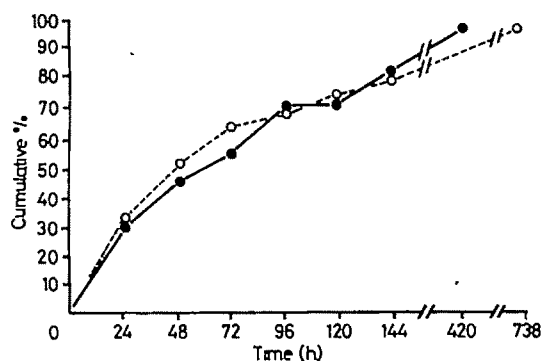


Fig. 1 Time from onset of symptoms to death for patients with myocardial rupture (●) and control group A (non-rupture cardiac death) (○).

pericardial origin not responding to other treatment.

STATISTICAL METHODS

Two controls with acute myocardial infarction were selected and matched for age and sex for each patient with myocardial rupture, one who had died in hospital but not from rupture (non-rupture cardiac death) (control group A) and one who had survived the hospital stay (control group B). The controls were

selected from the next two patients in the consecutive patient register after the patient with rupture who fulfilled the matching criteria. The three groups were compared by Fisher's two tail exact test. Statistical significance was defined as $p < 0.05$.

Results

MORTALITY

A necropsy was performed in 75% of all fatal cases with acute myocardial infarction. Table 1 shows the numbers of patients with acute myocardial infarction, deaths, and myocardial ruptures. The total hospital mortality was 19% and was highest among women over 70 years (29%). Rupture through the free wall ($n=46$) or the septum ($n=5$) was found at necropsy in a total of 51 patients and at operation in another five (28 men and 28 women). Rupture was found in 17% of the hospital deaths, or 3.2% of all patients with acute myocardial infarction. Women aged <70 had the highest incidence of rupture, 42% of hospital deaths being due to rupture. The mean age of patients with rupture and the controls was 70.5 years. Figure 1 shows the time from the onset of symptoms to death for patients and controls. The median time from

Table 2 Clinical history before admission and clinical observations during admission of patients with myocardial rupture, and controls (group A, non-cardiac death rupture; group B, survivors) ($n=56$ in each of the three groups). Figures are numbers of subjects

Clinical characteristics	Patients	Control group A	Control group B	Statistical comparison (p value)		
				Patients vs group A	Patients vs group B	Group A vs group B
Characteristics						
Previous myocardial infarction	8	29	16	<0.001	NS	<0.05
Hypertension	23	27	28	NS	NS	NS
Angina (duration).						
<2 months	42	19	32	<0.001	NS	<0.05
>2 months	14	37	24	<0.001	NS	<0.05
Diabetes (treatment)						
Diet or tablets or both	8	14	7	NS	NS	NS
Insulin	1	3	2	NS	NS	NS
Previous treatment with corticosteroids	3	5	5	NS	NS	NS
Beta blocker treatment on admission	18	27	24	NS	NS	NS
Observations						
Sustained hypertension	8	4	15	NS	NS	<0.05
Sustained hypotension	18	39	8	<0.001	<0.05	<0.001
Shock	10	35	0	<0.001	<0.01	<0.001
Intravenous or oral treatment with beta blockers	20	24	29	NS	NS	NS
Inhospital corticosteroid treatment	12	8	3	NS	<0.05	NS
Heart failure:	37	50	34	<0.01	NS	<0.001
Mild	25	15	23	NS	NS	NS
Severe	12	35	11	<0.001	NS	<0.001
Antiarrhythmic treatment	21	33	21	<0.05	NS	<0.05
Infarct site (main):						
Anterior	31	23	20	NS	NS	NS
Posterior	23	23	27	NS	NS	NS
Septal	1	1	0	NS	NS	NS
Apical	1	2	0	NS	NS	NS
Subendocardial	0	6	2	<0.05	NS	NS
Unclassified	0	1	7	NS	<0.05	NS
Mean (SEM) maximum serum AST activity (μKat/l)	7.95 (2.45)	6.79 (2.60)	2.88 (0.27)			

NS, not significant; AST, aspartate aminotransferase.

Conversion: SI unit to traditional unit—aspartate aminotransferase: $59.9 \mu\text{Kat} \approx 1 \text{ U}$ ($1 \mu\text{Kat} \approx 1 \mu\text{mol/s}$)

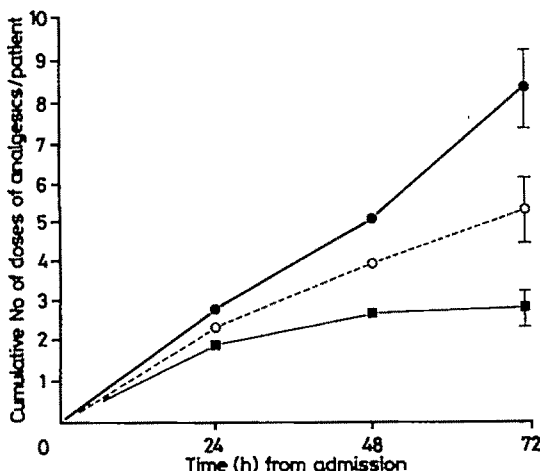


Fig. 2 Cumulative number of doses of analgesics per patient in relation to time (h) from hospital admission for patients with myocardial rupture (●), control group A (non-rupture cardiac death) (○), and control group B (survivors) (■).

admission to death was approximately 50 hours for patients and control group A (non-rupture cardiac death). Thirty per cent of the ruptures occurred within 24 hours after the onset of the initial symptoms.

CLINICAL HISTORY

Angina and previous acute myocardial infarction were more common among control group A (Table 2). Patients and control group B (survivors) were in most cases relatively free of previous cardiovascular or other disease—for example, chronic angina pectoris (>2 months) and previous myocardial infarction. On the other hand, angina of recent onset (<2 months before infarction) was more common among patients and control group B than among control group A.

CLINICAL FINDINGS DURING ADMISSION

Table 2 also shows some clinical findings recorded during hospital admission for the three groups. Sustained hypertension while in the coronary care unit was more common among patients than among control group A. Generally, hypertension was associated with survival, whereas hypotension and shock were associated with death. The majority of patients and control group B had normal blood pressure during their hospital stay. During the time in the unit more patients received moderate amounts of corticosteroids intravenously than the two control groups. The vast majority (79%) of the patients who subsequently ruptured did not receive any corticosteroids at all during the hospital stay.

Severe heart failure and antiarrhythmic treatment were uncommon among patients compared with control group A. No clear cut differences between the three groups as to the site of the infarction could be seen. The controls in group A had large infarcts as estimated by the peak serum aspartate aminotransferase activity, but even higher peak values were obtained in the patient group, being significantly higher than those in control group B ($p < 0.05$).

The degree and duration of chest pain was estimated by determining the cumulated individual number of analgesic injections during the hospital stay (Fig. 2). Patients received analgesics approximately three times a day without any tendency towards a decrease throughout their stay. Controls in group B received analgesics during the first 24 hours but very few after that. The differences after three days were significant for all three groups ($p < 0.05$).

Discussion

The introduction of coronary care units has decreased hospital mortality in cases of acute myocardial infarction. This residual mortality is mainly due to infarctions affecting more than 40% of the myocardium, which lead to severe pump failure and refractory arrhythmias. The second most common cause of in-hospital death is myocardial rupture. Primary ventricular fibrillation is no longer an important cause of in-hospital deaths.¹

In published reports myocardial rupture is commonly divided into four groups: rupture of the papillary muscles, the interventricular septum, and the free wall (acute and subacute rupture). Rupture of the papillary muscles leading to acute mitral incompetence with >90% mortality¹⁰ was very rare in our study, the incidence being only 1.5% of in-hospital deaths or 8% of all ruptures. Similar figures have been reported by others (Table 3). Rupture of the interventricular septum is apparently more common, between 10% and 20% of all ruptures occurring through the septum.^{2,4,5} In our study the figure was 16%. Without surgical treatment 50% of these patients have been reported to die within the first week and 85% within two months.^{13,14} Surgical correction of this condition is often possible, and patients undergoing successful operation seem to have a relatively good prognosis.¹³ There is a great deal of controversy as to the optimal time of surgical intervention, although recent studies suggest a more favourable outcome if surgery is performed within 24 hours.¹² Acute rupture of the free wall is by far the most common type of rupture, comprising about 50% of all ruptures. Successful surgical intervention has been reported, always including rapid pericardiocentesis, volume expansion, and

Table 3 Incidence of myocardial rupture at different sites

Study	% Of all ruptures involving:			Total No
	Papillary muscles	Septum	Free wall	
Zeman and Rodstein ¹¹	6	0	94	16
van Tassel and Edwards ²	17.5	20	62.5	40
Feneley <i>et al</i> ¹²	8	67	25	49
Present study	8	16	75	61

immediate subsequent surgery using cardiopulmonary bypass.¹⁵⁻¹⁷ Subacute rupture of the free wall was described in 1973 by O'Rourke, who reported two cases of rupture of the free wall in which severe hypotension and shock were present for several hours after diagnosis but before death or surgical intervention.¹⁸

According to our findings as well as those of others, patients suffering a myocardial rupture are previously healthy compared with other victims of in-hospital deaths.^{19,20} In the present study the prevalence of hypertension, diabetes, angina, and previous myocardial infarction was as high among patients with rupture as among survivors but lower than that among the control group with non-rupture cardiac death. Thus we cannot agree with previous investigators who have claimed that the absence of previous cardiovascular disease would predispose to heart rupture.^{20,21} Such a statement seems valid only when other in-hospital deaths rather than survivors served as controls.

The incidence of myocardial rupture as well as the age and sex distribution in our study are consistent with those in other studies.^{3,8} We also agree with others that women have a higher risk of rupture of the free wall. Prolonged and recurrent chest pain has often been considered to be the most frequent and consistent clinical characteristic of myocardial rupture,^{8,19} which agrees with our findings.

Corticosteroid treatment has been held responsible for defective healing and scar formation predisposing to cardiac rupture. The basis for this seems to be a case report²² of a single patient who developed a ven-

tricular aneurysm after receiving corticosteroids for 53 days. Roberts *et al* have reported a trial in which very large doses of methylprednisolone were given repeatedly in accordance with a non-randomised protocol to 12 patients, of whom five died. Two of the victims had rupture of the ventricular septum.⁷ In our study patients who subsequently ruptured received steroids more often than controls. We believe that this was due to their persistent or recurrent chest pain often being interpreted as a sign of pericarditis and therefore treated with small doses of prednisolone (5-10 mg/day). Nevertheless, since 79% of patients who ruptured did not receive any steroid treatment at all defective healing due to corticosteroid treatment seems to play only a minor role, if any, in the pathogenesis of myocardial rupture.

Hypertension has been considered by several authors as an important pathogenetic factor.^{5,9,20} We believe that this is a misconception due to the lack of adequate controls. When cardiac death due to rupture is compared with non-rupture cardiac death, hypertension will indeed be more common among the victims with rupture. But the highest frequency of hypertension occurs among patients who survive their infarction. Sustained hypertension may thus be regarded as a sign of better preserved left ventricular function.

It is important to remember that because of the time course of myocardial rupture and the methods used the present study is subject to some bias. Because of the short period of in-hospital observation for cases of rupture the true prevalence of most clinical findings among these cases tends to be underestimated, not only compared with those among survivors. Therefore the observed differences between patients with rupture and survivors underestimate the importance of such differences with regard to sustained hypotension, shock, in-hospital treatment with steroid, antiarrhythmic medication, and enzyme activity. In view of the details of the findings the importance of any of the analysed differences is less likely to be overestimated.

Since 1973, when O'Rourke introduced the term subacute heart rupture,¹⁸ several reports of successful surgical treatment of patients with apparently subacute heart rupture have been published.²³ Clinically, these patients have generally been severely hypoten-

Table 4 Incidence of subacute myocardial ruptures

	% Of all ruptures with signs of subacute rupture*	% Of ruptures as % of all fatal AMI
Zeman and Rodstein ¹¹	20	19
London and London ⁸	34	4.7
Lautsch and Lanks ²³	34	
	(65)	7.3
Lewis <i>et al</i> ⁶	21	8.6
Rasmussen <i>et al</i> ¹³	16	12.6
Feneley <i>et al</i> ¹²	41	—
Present study	32†	17

*Sustained hypotension, sudden fall in blood pressure, thrombus formation at necropsy (progressive scarring at necropsy).

†Corresponds to patients with sustained hypotension (Table 2). AMI, acute myocardial infarction.

sive, often in shock, with severe right sided heart failure and sometimes, but not very often, showing classical signs of pericardial tamponade. It has been suggested¹⁹ that this condition might be more readily diagnosed at an early stage by echocardiography, since this technique can detect very small amounts of fluid (15–20 ml) in the pericardial sack.²⁴

Table 4 shows previous studies together with the present series in which data indicate the presence of subacute heart rupture. Sustained hypotension, shock, sudden fall in blood pressure, or thrombus formation at the site of rupture have been regarded as indicating subacute rupture. As many as 30% of all ruptures may be subacute.

There is a need for further studies directed towards the treatment and, if possible, prevention of myocardial rupture. These should aim at evaluating techniques for diagnosis before death and at investigating patients with the highest risk of rupture—that is, women <70 years of age with sustained chest pain suffering their first myocardial infarction. Therapeutic interventions should also be evaluated. Because of the nature of myocardial rupture of the free wall, however, treatment has to be directed towards prevention—that is, reduction in infarct size.

We thank Anders Odén for the statistical analyses. The study was financially supported by AB Hässle, subsidiary to Astra Pharmaceuticals AB, Mölndal, Sweden.

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Effect of xamoterol (ICI 118587), a new β_1 adrenoceptor partial agonist, on resting haemodynamic variables and exercise tolerance in patients with left ventricular dysfunction

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SUMMARY The effect of xamoterol, a β_1 adrenoceptor partial agonist, on resting haemodynamic measurements and exercise tolerance was studied in 10 patients with dyspnoea of effort. All patients had poor left ventricular function due to myocardial infarction with ejection fractions ranging from 15% to 35% (mean 28%). The cardiac index and stroke work index both rose significantly. The mean pulmonary artery pressure fell from 20(2) mm Hg to 16(2) mm Hg and pulmonary artery wedge pressure from 14(2) mm Hg to 10(2) mm Hg within the first four hours. Exercise tolerance, measured on the treadmill, increased significantly in seven patients but was unchanged in the three who had the lowest left ventricular ejection fractions. Exercise heart rate response was attenuated by the drug in all patients.

It is concluded that xamoterol may be beneficial in patients with poor left ventricular function but can be harmful in extremely poor left ventricular function where high sympathetic drive may be important.

Xamoterol {(+/-)-1-(4-hydroxyphenoxy)-3-[2-(4-morpholine carbonamido)ethylamino]-propan-2-ol fumarate} has been shown in animal experiments to be a β_1 adrenoceptor partial agonist with little effect on arterial impedance.¹ Its partial agonist or intrinsic sympathomimetic activity amounts (at its maximum) to 45% of the maximum activity of the full agonist isoprenaline.² Previous studies in volunteers showed that at rest it has positive inotropic properties as indicated by shortening of the systolic time intervals and rise in systolic blood pressure.³ It attenuates the chronotropic response to exercise.^{4,5} The beneficial haemodynamic effect of xamoterol in patients at rest with left ventricular dysfunction has been reported recently.⁶ Nevertheless, there is no information about the effect of this drug on exercise tolerance, which is a measurement of practical importance.

We studied the effect of xamoterol on resting haemodynamic variables and exercise tolerance in patients with exertional dyspnoea caused by angio-

graphically confirmed myocardial infarction. The study was single blind; xamoterol was given for two weeks followed by placebo for two weeks and finally xamoterol for four weeks. Effort tolerance was measured before treatment and fortnightly thereafter. Haemodynamic measurements were made before and after the first dose of xamoterol and after eight weeks' treatment with xamoterol.

Patients and methods

PATIENT POPULATION

Ten patients (nine men and one woman), whose mean (SD) age was 54 (2.4) years, were studied. They all had chronic left ventricular dysfunction and dyspnoea of effort (New York Heart Association (classes II and III)). Their mean angiographic left ventricular ejection fraction was 28% (range 15-35%). Two patients (cases 6 and 8) also had moderately severe mitral regurgitation. Table 1 shows the patients' characteristics and treatment at the start of the study. These treatments had failed to improve their symptoms. Vasodilative and antiarrhythmic agents were withdrawn at least two weeks before the start of the study. A prestudy exercise test was performed to determine a suitable exercise protocol for each patient. As a result either

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Accepted for publication 12 February 1985

Table 1 Patient characteristics and treatment at the start of the study

Case No	LVEF (%)	Coronary angiography	Medical treatment (mg daily)
1	15	LAD blocked, Cx and RCA stenoses	Fruzemide 120
2	22	LAD blocked, Cx and RCA stenoses	Fruzemide 80; amiloride 10
3	32	LAD and Cx stenoses, RCA blocked	Fruzemide 80
4	32	LAD and Cx stenoses, RCA blocked	Fruzemide 80; bendrofluazide 5
5	35	LAD and Cx stenosis, RCA blocked	Fruzemide 80
6	30	LAD, Cx, and RCA stenoses	Fruzemide 120, lanoxin 0.25; amiloride 10
7	26	LAD blocked, RCA and Cx stenoses	Fruzemide 80
8	33	LAD, RCA, and Cx stenoses	Fruzemide 250, spironolactone 200
9	18	LAD blocked, RCA stenosis	Fruzemide 80
10	35	RCA blocked, LAD and Cx stenoses	Fruzemide 80

LVEF, left ventricular angiographic ejection fraction; LAD, left anterior descending; RCA, right coronary artery; Cx, circumflex coronary artery.

the standard or modified Bruce protocol⁷ was chosen for each patient.

EXERCISE TEST PROCEDURE

Exercise tolerance was assessed approximately 24 hours before the haemodynamic study using the Marquette Case TM Computer Assisted System for Exercise (Marquette Electronics Inc, Milwaukee, USA) using the standard Bruce or a modified Bruce protocol. A maximal symptom limited exercise test was performed. Exercise performance was calculated as the sum of work done during each stage of the Bruce protocol (Fig. 1). Work done during each stage of this exercise protocol may be expressed as follows: work done equals $Mg (\sin \theta + \cos \theta) (S) (T)$ in Joules, where θ is the angle of inclination of the treadmill; S the speed of the treadmill in m/s; T the time spent on each stage of exercise in seconds; g the gravitational force (9.8 m/s^2); and M the mass of the patient in kg. Modified lead V1, V5, and aVF electrocardiograms were recorded continuously during the test.

RESTING HAEMODYNAMIC MEASUREMENTS

Early—On the first day of the study right heart catheterisation was performed at rest, with the patient

supine and without premedication, using a flow directed thermodilution catheter. Baseline measurements of pulmonary artery systolic and diastolic pressure, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, and heart rate were recorded. Cardiac output was measured in triplicate using a Gould Cardiac Index Computer Model SP1435 (Gould Inc., Oxnard, USA). Systemic arterial pressure was measured by a standard sphygmomanometer. Electrocardiographic monitoring was maintained throughout the study. After the baseline haemodynamic variables were measured xamoterol 200 mg was given orally and the measurements repeated 1, 2, 4, 6, and 12 hours later.

Late—During the eighth week of the trial right heart catheterisation was repeated at rest with the patient supine, without premedication, and before the morning dose of xamoterol. After the baseline haemodynamic variables were measured xamoterol 200 mg was given orally and the measurements repeated one and two hours later.

OUTPATIENT TREATMENT

Outpatient treatment was continued with xamoterol orally 200 mg twice daily. Clinical examination and exercise tolerance testing were repeated at fortnightly intervals. During the third and fourth weeks patients were changed to treatment with the placebo.

DERIVED-HAEMODYNAMIC VARIABLES

Mean systemic arterial blood pressure (MAP) was calculated as: diastolic pressure plus $1/3$ (systolic minus diastolic pressures) in mm Hg; body surface area in m^2 was determined from standard tables from their height and weight; cardiac index (CI) was calculated as CO/BSA (l/min per m^2), where CO is cardiac output (l/min); stroke volume index (SVI) as: $(\text{CO} \times 1000)/\text{BSA} \times \text{HR}$ (ml/beat/m^2), where HR is heart rate (beats/min); left ventricular stroke work index (LVSWI) as: $(\text{MAP}-\text{PCWP}) \times \text{SVI} \times 0.0136$ (g m/m^2), where PCWP is pulmonary capillary wedge pressure; and systemic vascular resistance (SVR) as: MAP

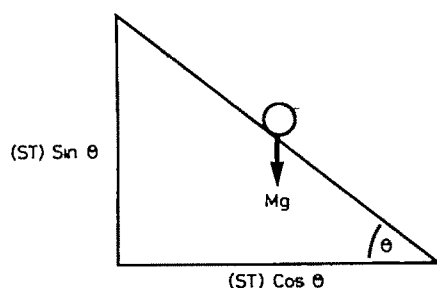


Fig. 1 Exercise performance calculated as sum of work done (Mg) during each stage of protocol: $Mg (\sin \theta + \cos \theta) (S) (T)$ (Joules), where θ , angle of inclination (of treadmill); S , speed (of treadmill) m/s; T , time spent on each stage of exercise (s); g , gravitational force (9.8 m/s^2); M , mass of patient (kg).

Table 2 Haemodynamic indices in 10 patients before and after a single oral dose of xamoterol 200 mg. Values are mean (SEM)

Haemodynamic indices	Pretreatment value	Peak value	Time of peak response (h)	p value
Mean systemic arterial pressure (mm Hg)	91(4)	88(4)	4	NS
Heart rate (beats/min)	69(6)	76(5)	4	NS
Pulmonary capillary wedge pressure (mm Hg)	14(2)	10(2)	1	<0.01
Mean pulmonary artery pressure (mm Hg)	20(2)	16(2)	4	<0.001
Cardiac index (l/min per m ²)	2.3(0.1)	3.2(0.2)	4	<0.001
Stroke volume index (ml/beat/m ²)	40(3)	46(3)	4	<0.0005
Systemic vascular resistance (dyn s cm ⁻⁵)	1693 (59)	1247(124)	4	<0.01
Left ventricular stroke work index (g m/m ²)	45(4)	53(5)	4	<0.0025

$\times 80$)/CO (dyn s cm⁻⁵. All results are expressed as mean (standard error of mean (SEM)) and analysed using Student's paired *t* test.

Results

RESTING HAEMODYNAMIC VARIABLES

On administration of the drug there was an increase in cardiac index and a fall in pulmonary artery pressure. Maximum change in the haemodynamic variables occurred within four hours of giving xamoterol (Table 2 and Figs. 2-4). The drug increased both cardiac index and stroke volume index from 2.3(0.1) to 3.2(0.2) l/min per m² ($p < 0.001$) and from 40(3) to 46(3) ml/beat/m² ($p < 0.0005$) respectively (Fig. 4 *a* and *b*). Left ventricular stroke work index (Fig. 4 *d*) was increased from 45(4) to 53(5) g m/m² ($p < 0.0025$) while systemic vascular resistance fell from 1693(59) to 1247(124) dyn s cm⁻⁵ ($p < 0.01$) (Fig. 4 *c*).

The maximum change in mean pulmonary artery pressure from 20(2) mm Hg to 16(2) mm Hg occurred at four hours ($p < 0.001$) and in pulmonary capillary wedge pressure from 14(2) mm Hg to 10(2) mm Hg at one hour ($p < 0.01$) (Table 2, Fig. 2).

Heart rate was not significantly altered in the group as a whole, the control heart rate being 69(6) beats/min and 76(5) at four hours (Table 2). Nevertheless, in the seven patients who subsequently showed an improvement in exercise tolerance the heart rate rose from 69(6) to 80(5) beats/min at four hours ($p < 0.05$) (Fig. 3 *a*).

EXERCISE TESTING

All patients had appreciably impaired exercise tolerance before treatment (Fig. 5, Table 3). After two weeks' treatment with xamoterol there was a significant improvement in exercise tolerance in seven patients ($p < 0.05$) (Fig. 3). One patient failed to show

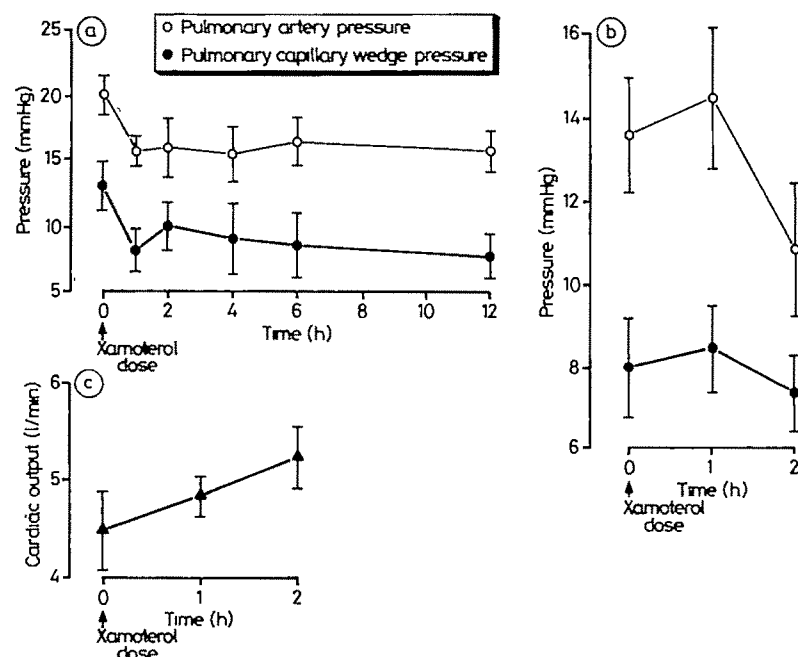


Fig. 2 Resting haemodynamic variables after a single oral dose of xamoterol on (a) the first day and (b) in the eighth week; (c) resting cardiac index after a single oral dose of xamoterol in the eighth week. Values are mean (SEM).

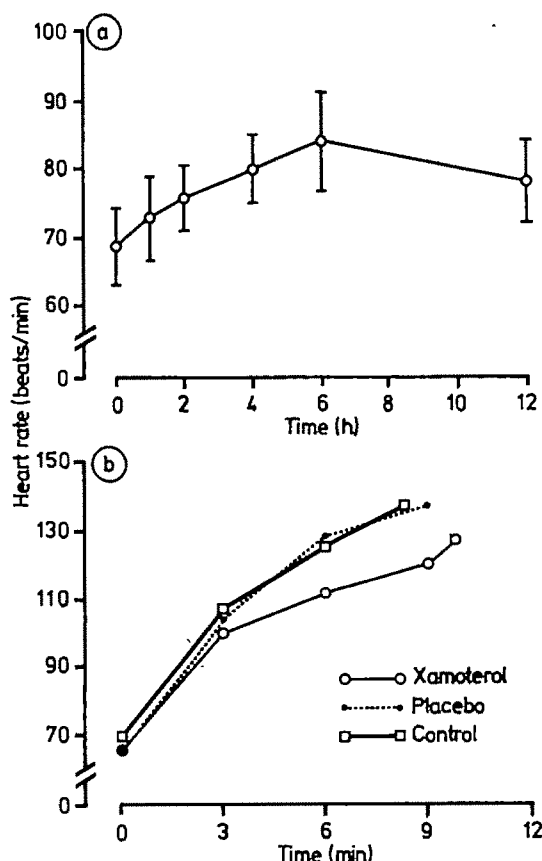


Fig. 3 Heart rate response to a single oral dose of xamoterol (a) at rest and (b) during exercise. Values are mean (SEM).

an improvement in exercise tolerance. Two had stopped treatment before two weeks; one because of nausea and the other on his own initiative because of lack of subjective improvement in symptoms. With placebo the exercise tolerance fell to pretreatment levels in six patients whose exercise tolerance had improved on the drug. It was unchanged in two patients. When xamoterol was restarted there was an improvement in exercise tolerance in the six patients who had deteriorated with placebo and in one of the patients who showed no change in exercise tolerance with placebo. The condition of the other patient who showed no change with placebo deteriorated and he was withdrawn from the study after a further two weeks of xamoterol.

The change in exercise tolerance with the drug was significantly greater than that with placebo ($p < 0.05$) (Table 3). The increase in heart rate with xamoterol after maximal exercise was significantly lower than that with placebo ($p < 0.05$) (Fig. 3 b).

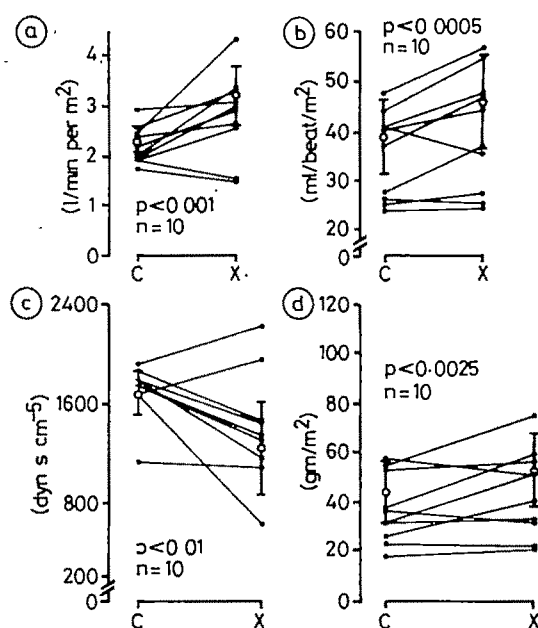


Fig. 4 Haemodynamic variables before (C) and after (X) peak response to a single oral dose of xamoterol: (a) cardiac index; (b) stroke volume index; (c) systemic vascular resistance; and (d) left ventricular stroke work index.

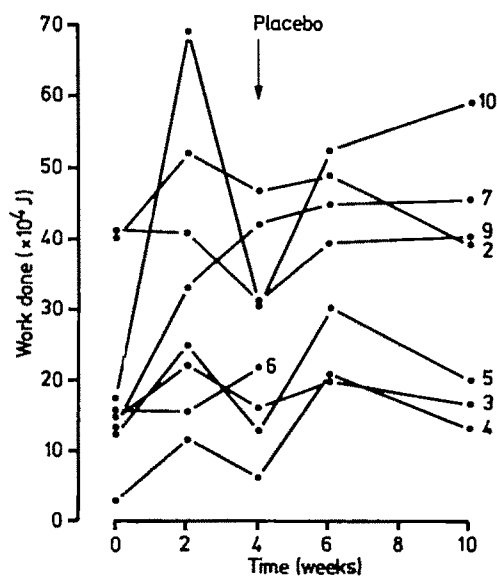


Fig. 5 Changes in exercise tolerance in the 10 patients during long term administration of xamoterol and placebo. Numbers are case numbers.

Table 3 Exercise tolerance in study patients. Values are mean (SEM)

Time (weeks)	Treatment given	Work done ($J \times 10^4$)	p value (n)*
0	Baseline	20.0(4.8)	(10)
0-2	Xamoterol 200 mg twice daily	34.1(6.9)	<0.05(8)
2-4	Placebo	26.7(5.2)	(8)
4-6	Xamoterol 200 mg twice daily	39.7(4.9)	<0.05(7)
6-10	Xamoterol 200 mg twice daily	33.6(6.5)	<0.05(7)

*Significance levels derived from comparison of exercise tolerance with placebo and xamoterol.

Discussion

Previous work suggests that there is increased activity of the sympathetic system as well as changes in the renin-angiotensin and vasopressin neurohumoral systems in chronic heart failure.⁸ These pathophysiological derangements occur to varying degrees in different patients. Xamoterol has been shown to have 40% of the chronotropic and inotropic effects of the pure agonist isoprenaline.² During exercise it reduces the chronotropic response to sympathetic stimulation.^{4,9} It therefore shows both beta adrenoceptor agonism and antagonism, depending on the prevailing level of sympathetic activity; it is a beta₁ adrenoceptor partial agonist.

This study shows that xamoterol can improve resting haemodynamic variables and exercise tolerance in some patients with pronounced impairment of left ventricular function caused by myocardial infarction. At low levels of sympathetic activity it acts as a beta₁ adrenoceptor agonist as shown by the increase in stroke volume, left ventricular stroke work index, and heart rate and the fall in pulmonary capillary wedge pressure that occurred in most patients. The fall in systemic vascular resistance is probably the result of increased cardiac output promoting a reduction in endogenous sympathetic activity rather than a direct vasodilator action. Certainly, work in animals has shown that the drug is not a vasodilator. It is likely that in the two patients in whom the drug did not have a positive inotropic or positive chronotropic effect sympathetic tone was higher and the drug acted as a beta adrenoceptor antagonist. These two patients had the lowest ejection fractions of the group.

The patients in whom the drug caused a positive chronotropic effect at rest experienced an improvement in exercise tolerance, whereas those in whom the drug had a negative chronotropic effect and who presumably had higher levels of sympathetic activity at rest did not benefit in terms of exercise tolerance.

The results from this small study suggest that whereas the drug can be given safely and with benefit

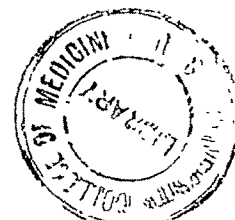
to patients with poor left ventricular function (mean ejection fraction 28%) it may be harmful to patients with extremely poor ventricular function who depend on high levels of sympathetic nervous system activity.

We thank Mr Eric B Faragher for statistical assistance.

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P 25, 729



How important is a history of chest pain in determining the degree of ischaemia in patients with angina pectoris?

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SUMMARY Since therapeutic decisions in patients with angina pectoris are usually based on the reported frequency of exertional and rest pain the relations between the historical frequency of chest pain and objective evidence of myocardial ischaemia during normal daily activity were investigated in 100 patients by 48 hour ambulatory ST segment monitoring. Of these 100 consecutive patients with chest pain, 91 had typical pain and nine some atypical features. Twenty six patients had normal coronary arteries and 52 of the 74 with significant coronary disease had ambulatory ST segment changes. There was no relation between the frequency of reported exertional or rest pain and (a) the severity of coronary artery disease or (b) the frequency of daytime or nocturnal ST segment changes. Twelve patients had nocturnal ST segment changes but only four complained of nocturnal angina. Most patients had both painful and painless episodes of ST segment changes, but a substantial number had either painless or painful episodes only. These differences were not related to the severity of coronary artery disease. Chest pain after the onset of ST segment change was perceived with wide interpatient and inpatient variability.

Thus the frequency of pain is a poor indicator of the frequency of significant cardiac ischaemia. Individual differences in the perception of pain may be more important.

One of the earliest descriptions of the clinical syndrome of angina pectoris was by Heberden in 1772.¹ Later, pathological studies showed the frequent association between angina pectoris and obstructive coronary artery disease.² More recent studies, however, have underlined the poor correlation between the frequency and distribution of anginal chest pain and the severity of underlying coronary artery disease.³⁻⁶ Although these studies compared the subjective symptoms of chest pain with the anatomical features of the coronary arteries, no correlations have been found between the frequency of chest pain and objective indices of myocardial ischaemia in patients with varying severity of coronary artery disease.

Reversible changes in the ST segment have been shown to coincide with periods of myocardial ischaemia, but these may or may not be accompanied by anginal pain in patients with or without underlying obstructive coronary artery disease.^{7,8} Recent

improvements in ambulatory electrocardiographic recording systems have enabled us to observe changes in the ST segment during the patient's normal daily activities.⁹ The relation between the occurrence of chest pain and the appearance of myocardial ischaemia (ST segment shifts) in patients with varying severity of coronary artery disease can thus be studied.

This study was designed to investigate the relation between the historical frequency of chest pain and myocardial ischaemia as determined by ambulatory electrocardiographic ST segment monitoring.

Patients and methods

STUDY POPULATION

One hundred consecutive patients (74 men, 26 women; mean (SD) age, 53.2(9) years) referred to one consultant cardiologist at this hospital and undergoing diagnostic coronary arteriography for chest pain were investigated. Patients with severe conduction defects or gross left ventricular hypertrophy on the electrocardiogram, atrial fibrillation, severe valvar heart

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Accepted for publication 19 March 1985

disease, and taking digoxin were excluded. Evidence of an old transmural myocardial infarction with electrocardiographic Q waves was present in 27 patients, and there were resting ST-T wave changes in a further 21. Informed consent was obtained from every patient.

CHEST PAIN

All patients complained of chest pain. Important features in the patients' history were particularly noted.

Typical angina pectoris denoted pain anywhere in the chest with or without radiation, occurring on exertion and relieved promptly with rest or sublingual nitrates. The pain was often associated with other precipitating factors and sometimes occurred also at rest during the day.

Atypical angina pectoris denoted pain that was suggestive of myocardial ischaemia but had some atypical features.

Resting or nocturnal angina pectoris or both denoted typical anginal chest pain occurring not only during exertion but also at rest during the day or wakening the patient at night.

STUDY PROTOCOL

After hospital admission all antianginal medication was withdrawn 48 hours before further investigations were started. Glyceryl trinitrate was given for chest pain. Unless the patient complained of chest pain with minimal activity, he was encouraged to be mobile inside and outside the hospital. Ambulatory electrocardiographic ST segment monitoring was performed for 48 hours, during which time the patients kept angina diaries. They noted the time of onset of chest pain and the activity at the time of pain during the period of ambulatory monitoring.

AMBULATORY MONITORING

A two channel recording was obtained using two pairs of bipolar electrodes which were applied precordially to record lead CM5 in the first channel. Inferior changes were recorded in the second channel using a lead resembling aVF in 35 patients and a lead resembling lead II in the other 65. A 48 hour two channel recording was obtained on magnetic tape using a frequency modulated recorder (Oxford Medilog 2, frequency response 0.05–40 Hz). The tapes were then visually analysed at 60 times normal speed (Oxford Medilog MA20 scanner), and areas of interest were printed out at 25 mm/s.

Significant ST segment depression was defined as planar or downsloping shift of the ST segment of ≥ 1 mm in magnitude 0.08 s after the J point. Significant ST segment elevation was defined as an upward shift of the ST segment of ≥ 1 mm in magnitude at the J point.

ANGIOGRAPHY

Conventional contrast left ventriculography and coronary arteriography were performed and a significant lesion was defined as a $\geq 70\%$ luminal narrowing in a major coronary artery. Left main stem stenosis was classed as two vessel disease. Five patients with normal coronary arteries and ambulatory ST segment changes had ergonovine provocation, in which a mean dose of 0.6 mg was given intravenously and the angiograms were repeated.

Results

Of the 100 patients, 26 had normal coronary arteries, 22 single vessel disease, 22 two vessel disease, and 30 three vessel disease. Seven patients had left main stem

Table 1 Subjective frequency of exertional and rest pain in patients with varying severity of coronary artery disease. Figures are numbers (%) of patients

Coronary disease	No of patients	Number of episodes:			
		>1/day	<1/day to >1/week	<1/week	None
Exertional pain					
No of vessels affected:					
0	26	8 (31)	5 (19)	13 (50)	0 (0)
1	22	10 (45)	5 (23)	7 (32)	0 (0)
2	22	9 (41)	4 (18)	9 (41)	0 (0)
3	30	18 (60)	5 (17)	7 (23)	0 (0)
Left main stem stenosis*	7	7 (100)	0 (0)	0 (0)	0 (0)
Pain at rest					
No of vessels affected:					
0	26	4 (15)	4 (15)	17 (65)	2 (5)
1	22	6 (28)	2 (9)	8 (36)	6 (28)
2	22	3 (14)	4 (18)	7 (32)	8 (36)
3	30	6 (20)	2 (7)	8 (27)	14 (46)
Left main stem stenosis*	7	2 (29)	1 (13)	2 (29)	2 (29)

*These patients are also included in the figures for two and three vessel disease.

Table 2 Subjective frequency of exertional and rest pain in patients with coronary artery disease and episodes of ST segment change (during daytime only and during daytime and at night) and in patients with no ST segment change. Figures are numbers (%) of patients

ST segment changes	No of patients	Number of episodes:			
		>1/day	<1/day to >1/week	<1/week	None
Exertional pain					
Daytime only	41	22 (54)	4 (10)	15 (36)	0 (0)
Nocturnal and daytime	11	6 (55)	3 (27)	2 (18)	0 (0)
None	22	9 (40)	7 (33)	6 (27)	0 (0)
Rest pain					
Daytime only	41	5 (12)	6 (15)	15 (37)	15 (36)
Nocturnal and daytime	11	3 (28)	0 (0)	4 (36)	4 (36)
None	22	4 (18)	3 (13)	8 (38)	7 (31)

stenosis. Ninety one patients complained of typical anginal pain and nine had atypical features. One patient with atypical chest pain had normal coronary arteries but the other eight had significant coronary artery disease.

Patients complained of pain of varying severity and type (Table 1). All suffered chest pain during exertion in the daytime, 70% also complained of rest pain of varying frequency, and 39% complained of nocturnal angina.

RELATION BETWEEN PAIN AND THE SEVERITY OF CORONARY ARTERY DISEASE

There was no correlation between the frequency of exertional or rest angina and the underlying coronary anatomy (Table 1). Thus 60% of patients with three vessel disease complained of frequent (>1 episode a day) exertional pain, and 31% of patients with normal coronary arteries also had frequent exertional pain. Similarly, frequent (>1 episode a day) rest pain occurred in 20% of patients with three vessel disease and also in 15% of patients with normal coronary arteries. All seven patients with left main stem stenosis complained of frequent exertional pain.

RELATION BETWEEN PAIN AND AMBULATORY ST SEGMENT CHANGE

Fifty one of the 74 (69%) patients with coronary

artery disease had episodes of transient ST segment depression and one had episodes of ST segment elevation and depression during 48 hours of ambulatory monitoring (Table 2). ST segment changes occurred during the daytime on exertion in all 52 patients with ambulatory ST segment changes, and nocturnal resting ST segment changes occurred in 11 (15%) of patients with coronary artery disease.

Table 2 compares the historical frequency of exertional and rest pain with the frequency of ambulatory daytime (exertional) and nocturnal (resting) ST segment changes. There was no correlation between the frequency of exertional or of rest pain and the frequency of observed daytime or nocturnal ST segment changes. Thus a history of frequent (>1 episode a day) exertional angina was obtained not only from 54% of patients with ambulatory ST segment changes but also from 40% of patients with no ambulatory ST segment changes after 48 hours of monitoring. Similarly, a history of infrequent (<1 episode a week) chest pain was obtained from 33% of patients who had ambulatory ST segment changes during 48 hours of monitoring. Almost 90% of 39 patients with varying frequency of nocturnal angina pectoris had no nocturnal ST segment changes during 48 hours of monitoring. When the historical frequency of rest pain was analysed, 75% of patients with frequent (>1 episode a day) pain had no nocturnal resting ST seg-

Table 3 Frequency of painful and painless episodes of ST segment change in patients with varying severity of coronary artery disease

Coronary artery disease	No of patients	% Of painful episodes	Number of patients:		
			With painful and painless episodes	With painful episodes only	With painless episodes only
Normal	5	8	1	0	4
Spasm only	1	39	1	0	0
No of vessels affected:					
1	11	31	5	4	2
2	17	48	5	4	8
3	24	29	14	6	4
Left main stem stenosis*	7	36	6	0	1

*These patients are also included in the figures for two- and three vessel disease.

Table 4 Comparison between the frequency, duration, and magnitude of painful and painless ST segment change in 24 patients with coronary artery disease and episodes of both painful and painless ST segment change. Values are mean (SD)

	Painful	Painless
No of episodes	4.3(4.7)	5.9(4.8)
Duration (mins)	24.5(31.5)	16(10)
Magnitude (mm)	2.1(1.1)	1.6(0.8)

ment changes, whereas 36% of the patients with nocturnal ST segment changes complained of no rest pain (Table 2).

ANALYSIS OF PAINFUL AND PAINFREE ST SEGMENT CHANGES

In 52 patients with coronary artery disease and ambulatory ST segment changes, a mean of 30% of all episodes of ST segment change recorded were associated with pain. In the five patients with normal coronary arteries and ambulatory ST segment depression, however, only one episode (8%) was accompanied by pain (Table 3).

In patients with coronary artery disease, 27% of patients had painful episodes of ST segment change only, 27% of patients had painfree episodes of ST segment change only, and 46% had both painful and painless episodes of ST segment change during monitoring. Nevertheless, there was no significant difference between the occurrence of painful or painfree episodes and the severity of underlying coronary artery disease (Table 3).

The characteristics of painful episodes of ST segment changes were compared with the painfree episodes in 24 patients who had both types of episodes during monitoring (Table 4). Painful episodes of ST segment change tended to be longer in duration and greater in magnitude than painless episodes, although these differences were not statistically significant.

ACTIVITY ANALYSIS

The activity at the time of chest pain was recorded by the 37 patients who also had ST segment changes on the electrocardiogram. Whereas 63% of these episodes were recorded as occurring during activities such as walking, shaving, or eating, 37% of the episodes occurred at rest during the day or at night. Chest pain was reported to occur a mean (SD) of 11(18) mins after the first onset of ST segment change, ranging from the time coinciding immediately with the onset of ST segment depression to 48 minutes after the onset of ST segment change. There was a wide intra-patient and interpatient variability in the time of onset of ST segment change on the electrocardiogram and the perception of chest pain.

Discussion

The patient's history of typical anginal chest pain is still regarded as one of the most sensitive indicators of the likelihood of the presence of significant coronary artery disease.¹⁰ It is, however, possible for myocardial ischaemia and true angina pectoris to occur in this group of patients as a result of localised coronary artery spasm,¹¹ which could be found in one of the six patients who had ambulatory ST segment changes. Two important points emerged from analysing this consecutive series of patients. Firstly, the clinical history of the type of frequency of chest pain was insufficient to identify the severity of underlying coronary artery disease (Tables 1-3). Secondly, ambulatory ST segment monitoring but not the history was able to identify the patient who had normal coronary arteries and coronary spasm.

Chest pain suggesting myocardial ischaemia can occur as a result of several non-cardiac conditions, and these may have been the cause in the vast majority of patients with normal coronary arteries. Nevertheless, 27% of patients with significant coronary artery disease also developed chest pain that was not associated with objective evidence of myocardial ischaemia (ST segment depression). A greater proportion of these patients, however, had episodes of ST segment change at other times associated with "similar" bouts of pain. These factors underline the difficulties of ascribing similar degrees of ischaemia to all episodes of pain complained of by the patient, as some episodes were associated with pronounced ST segment changes and others resulted in no change in the electrocardiogram. Although shifts in the ST segment of ≥ 1 mm in magnitude only were regarded as significant for ischaemia, care was taken to analyse the electrocardiogram when the patients complained of chest pain, and almost invariably no changes in the ST segment or T waves were observed.

Exertional angina is often treated with beta adrenoreceptor antagonists, which reduce myocardial oxygen demand at a given workload,¹² but ischaemia at rest is often treated with vasodilators.^{13,14} These therapeutic decisions in clinical practice are often based on the patient's history and factors precipitating pain. This study highlights the unreliability of the history in determining the extent and frequency of myocardial ischaemia during the day or at rest at night as this may lead to either overestimation or underestimation of the ischaemia.

Usually, the subjective frequency of chest pain underestimated the frequency of myocardial ischaemia¹⁵ in patients in whom ST segment changes were recorded. In fact, 14 patients had painfree episodes only. The reason why pain occurs with one episode of ST segment change and not another in the

same patient is still not fully understood. There is a suggestion from this series of patients and other reports¹⁵ that painful ischaemia is more profound in terms of either the size of myocardium involved or the duration of ischaemia. The perception of chest pain from the time of onset of the first change in the ST segment showed a considerable variation in the same patient and between individual patients. It is clear, therefore, that the occurrence of chest pain with ischaemia is dependent on individual factors as well as on the magnitude of underlying ischaemia.^{15,16}

Prognostic information is not as yet available for patients who have multiple episodes of painful and painless ST segment changes during normal daily activities,¹⁷ and long term studies are necessary to investigate the significance of asymptomatic myocardial ischaemia.

We thank the British Heart Foundation for their support.

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Ischaemic heart disease and prodromes of sudden cardiac death

Is it possible to identify high risk groups for sudden cardiac death?

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SUMMARY A study was carried out to determine the incidence of sudden cardiac death in a well defined population in relation to prodromes, medical history, and previous medical consultations before sudden cardiac death. In Frederiksborg county, Denmark (population 332 000), of 1309 consecutive deaths in a six month period, 166 were due to sudden cardiac death; among men aged 50-69, 22% of all deaths were due to sudden cardiac death. The incidence per 1000 population per year by age group (<50, 50-69, ≥70 years) was 0.19, 3.6, 11.4 in men and 0.12, 1.0, and 6.4 in women. The increasing incidence with age was significant. Ischaemic heart disease or hypertension had been recorded in 75% (124/166) of patients. Prodromes were reported in 54% (38/71) of patients with angina, and in 26% (25/95) without. Nineteen per cent (32/166) had neither prodromes nor overt heart disease. Forty six per cent of patients with known ischaemic heart disease and 24% without had consulted a doctor less than four weeks before death. Eight per cent had had a myocardial infarction within a year of death.

Cardiac death is the leading cause of death in most countries in the industrialised world and accounts for 20-30% of all deaths. Approximately 60-70%¹⁻³ of all cardiac deaths take place within 24 hours of the onset of acute symptoms and are often called sudden cardiac deaths. Sudden cardiac death is usually caused by ventricular arrhythmias with or without acute myocardial infarction.⁴

Sudden cardiac death is frequently the first manifestation of ischaemic heart disease.^{1,2} It may be preceded by acute myocardial infarction or angina pectoris.^{2,5} Furthermore, in patients admitted with suspected acute myocardial infarction, but in whom the diagnosis was ruled out, an increased risk of sudden death has been reported.^{6,7}

Several attempts have been made to lower the mortality from sudden cardiac death both by reducing risk

factors for ischaemic heart disease—for example, hypertension, hypercholesterolaemia, or smoking—in the general population,⁸ or in groups with increased risk factors,^{9,10} and also by giving beta blockers after acute myocardial infarction.⁵ Moreover, patients resuscitated in mobile coronary care units have been shown to have a good prognosis.^{11,12}

The purpose of this study was to determine the incidence of sudden cardiac death in relation to prodromes, previous clinical findings, and previous medical consultations in hospital and in general practice before sudden cardiac death.

Patients and methods

DEFINITIONS

In this study sudden death was defined as unexpected natural death occurring instantaneously or within 24 hours after the onset of acute symptoms or signs.¹³ The case was included if death was unwitnessed but likely to have fulfilled the above definition. Deaths among residents of nursing homes were not counted as sudden deaths. Sudden cardiac death was defined

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Accepted for publication 15 January 1985

Table 1 *Incidence of sudden cardiac death (SCD) in a six month period*

Age group (yr)	Population of area	Total No of deaths in six months	Total No of SCD in six months	SCD as % of death rate (95% CI)	Incidence of SCD per year per 1000 population (95% CI)
Men					
25-49	64 712	67	6	9.0 (3.4-18.5)	0.19 (0.18-0.20)
50-69	28 095	233	50	21.5 (16.8-26.3)	3.6 (3.5-3.7)
≥70	9 093	382	52	13.6 (10.2-17.0)	11.4 (11.2-11.6)
Women:					
25-49	63 032	41	4	9.8 (2.7-23)	0.12 (0.11-0.13)
50-69	28 151	133	14	10.5 (5.3-15.7)	1.0 (0.9-1.1)
≥70	12 445	418	40	9.6 (3.6-15.6)	6.4 (6.3-6.5)

CI, confidence interval.

as sudden death of which the cause was proved to be cardiac at necropsy or assumed to be cardiac because of clinical circumstances.

STUDY POPULATION

The basis for the study was all 218 cases of sudden death occurring between 1 May 1982 and 31 October 1982 in Frederiksborg County (population 332 000). A total of 1309 deaths had occurred during that period. Some of the cases were identified when reported to the coroner or following admission to any of the four regional hospitals. The remainder were identified from death certificates after careful checks with the doctor who had issued the death certificates. The diagnosis was based on necropsy findings in 118 cases and on death certificates in the remaining 100.

Of the 218 sudden deaths, 51 were of non-cardiac origin: 12 were due to pulmonary embolism, 21 to cerebrovascular disease, five to ruptured aortic aneurysm, four to gastrointestinal bleeding, three to asthma attacks, two to pneumonia, one to pulmonary carcinoma, one to epileptic seizure, and two to undetermined causes. In one case the general practitioner could not be identified. Thus the study population consisted of 166 cases of sudden cardiac death.

MEDICAL HISTORY

Information about prodromes, duration of fatal attack, and medical history was obtained from the coroner, police reports, hospital records, and from the patient's general practitioner, who in each case was asked to answer a standard questionnaire. Prodromes were defined as new symptoms or an aggravation of existing symptoms during the 14 days before death. Chest pain, dyspnoea, palpitation, and dizziness were classified as prodromes of cardiac origin. Systemic hypertension and congestive heart failure were considered to be present if the patient had been treated for either of these conditions. Previous admissions to coronary care units were noted. If an acute myocardial infarction had not been diagnosed such an admission was termed a "non-acute myocardial infarction episode."

STATISTICAL METHODS

The statistical methods used were the χ^2 test, Fisher's exact test, and a two sample *t* test. A *p* value of <0.05 was considered to be significant.

Results

Of 166 cases of sudden cardiac death, 58 were women (median age 76 (range 29-94) years) and 108 men (median age 67 (range 36-95) years). One hundred and eight deaths occurred at home, 27 after admission to hospital, five at work, four in ambulances, three during sporting activities, and 19 elsewhere.

One hundred deaths took place within one hour, 34 between one and six hours, and 32 between seven and 24 hours after the onset of acute symptoms. Sudden cardiac death accounted for 12.7% (95% confidence intervals, 10.9-14.6%) of all deaths. Sudden cardiac death was found more often in men (15.0%) than in women (9.7%) ($p<0.001$). In men it accounted for 22% of all deaths in the age group 50-59, significantly more than in elder and younger men ($p<0.01$) (Table 1). In women it accounted for approximately the same proportion of all deaths regardless of age (NS) (Table 1). In the middle aged (50-69 years) significantly more deaths among men than among women were due to sudden cardiac death ($p<0.01$); in the older and younger age groups the proportions were similar for men and women (NS). The incidence of sudden car-

Table 2 *Incidence of prodromes in two weeks before sudden cardiac death in relation to manifest ischaemic heart disease (angina pectoris, previous acute myocardial infarction, or chronic heart failure)*

	Total No of patients	Total No (%) with prodromes
Angina pectoris:		
Without	95	25 (26)
With	71	38 (54)
Ischaemic heart disease:		
Without	42	10 (24)
With	124	53 (45)
Total	166	63 (38)

} $p<0.01$ } $p<0.01$

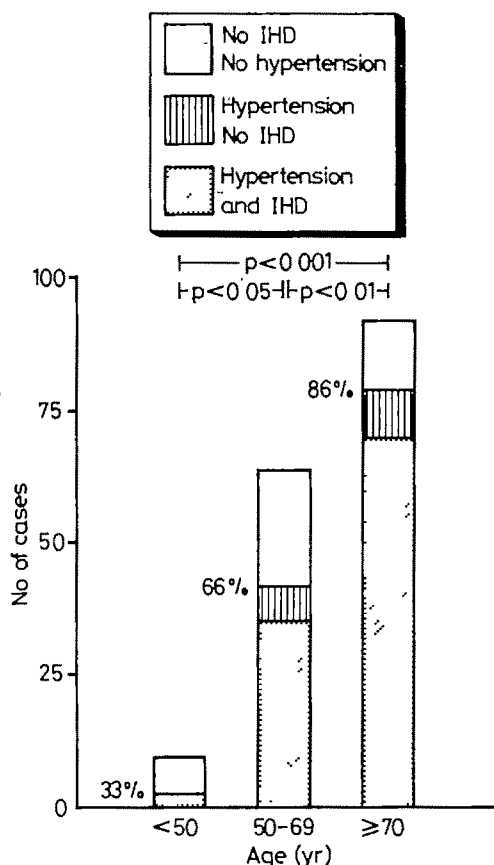


Fig. 1 Incidence of known ischaemic heart disease (IHD) with or without hypertension and presence of hypertension without IHD before sudden cardiac death in 166 cases by age group.

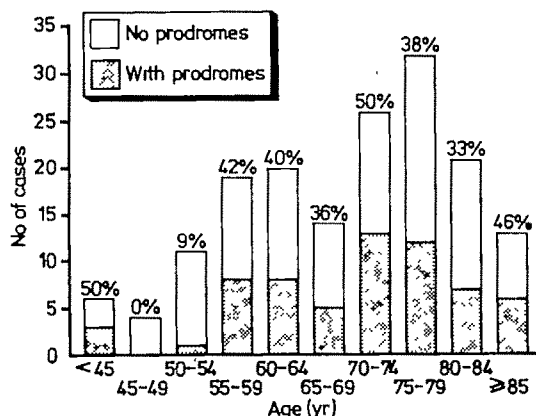


Fig. 2 Reported prodromes in the two weeks before sudden cardiac death in 166 cases in relation to age.

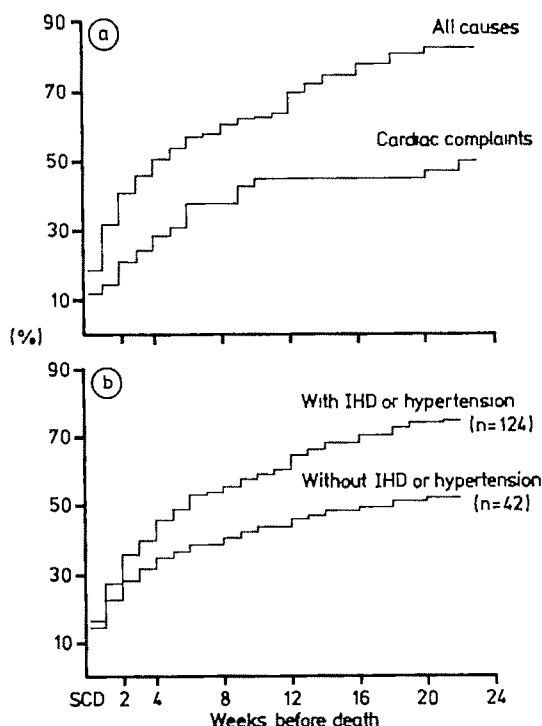


Fig. 3 Percentage of patients consulting a doctor in relation to time of sudden cardiac death in 166 cases; (a) shows all consultations and consultations for cardiac complaints alone and (b) all consultations for 124 patients with known ischaemic heart disease (IHD) (angina pectoris, previous acute myocardial infarction, or chronic heart failure) or hypertension or both and for 42 without.

diac death increased with age both for men and women ($p < 0.001$). For middle aged and older men the incidence was significantly higher than for women ($p < 0.01$) (Table 1).

ISCHAEMIC HEART DISEASE AND HYPERTENSION

A history of ischaemic heart disease or hypertension was recorded in 124 cases (44 women, 80 men) and was more common in the older age group (Table 2, Fig. 1). Thirty eight patients had angina pectoris, 30 congestive heart failure, 90 previous acute myocardial infarction, and 20 hypertension.

PRODROMES TO SUDDEN CARDIAC DEATH

Patients with ischaemic heart disease had prodromes more often than those without ischaemic heart disease (Table 2) ($p < 0.05$). This was due to a high prevalence of prodromes in patients with angina pectoris. When patients with angina pectoris are excluded there was no significant difference in the incidence of prodromes in patients with (36%) or without (23%)

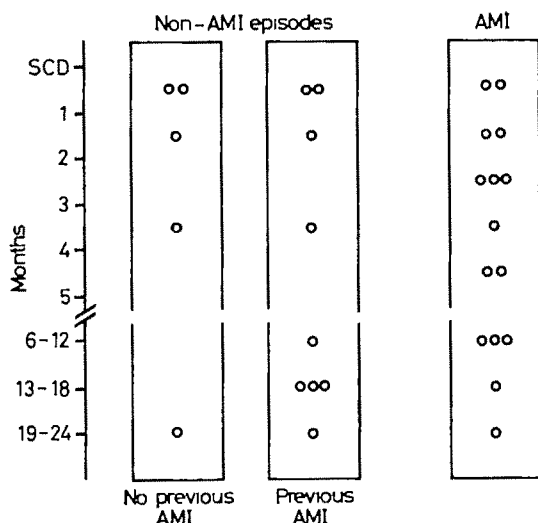


Fig. 4 Occurrence of acute myocardial infarction and non-acute myocardial infarction episodes in the two years before sudden cardiac death (SCD) in 166 cases. Non-acute myocardial infarction episodes (admissions with suspicion of acute myocardial infarction but not confirmed) are divided according to whether there was previous acute myocardial infarction.

ischaemic heart disease or hypertension or both (NS). The occurrence of prodromes was unrelated to age (Fig. 2) (NS).

RECENT MEDICAL CONSULTATION

Ninety six patients had seen a doctor within the two months before sudden cardiac death; 71 of these consultations were because of cardiac symptoms (Fig. 3a). Of the 124 patients with ischaemic heart disease or hypertension or both, 46% had seen a doctor within four weeks of death and, of the remaining 42 patients, 26% had seen a doctor during the same period ($p < 0.05$) (Fig. 3b).

ADMISSION TO CORONARY CARE UNIT

Non-acute myocardial infarction episodes were

Table 3 Incidence of hypertension or angina pectoris or both in relation to chronic heart failure in victims of sudden death who had had an acute myocardial infarction less than one year before death. Figures in parentheses are numbers receiving beta blockers

	Chronic heart failure		
	No	Yes	Total
Hypertension or angina pectoris or both			
No	1	1	2
Yes	1 (1)	10 (4)	11 (5)
Total	2 (1)	11 (4)	13 (5)

reported in 26 patients, 14 episodes occurring less than two years before death (Fig. 4), whereas acute myocardial infarction was diagnosed in 49 patients, 15 occurring less than two years before death (Fig. 4). Ten (6.0%) of the 166 patients had been in a coronary care unit less than two months before death. In 13 (7.8%) cases of sudden cardiac death acute myocardial infarction was recorded less than one year before death. Eleven had angina pectoris or hypertension, 10 of whom were treated for congestive heart failure and five received beta blockers (Table 3).

Discussion

Sudden cardiac death is an important cause of death in middle aged men, among whom almost a quarter of all deaths are due to sudden cardiac death. This accords with the established fact that death due to ischaemic heart disease is the main cause of death in this group.

The incidence of sudden cardiac death in this study (as given in Table 1) corresponds well with that in the study of Romo from Helsinki even though he included only cases of sudden death occurring within one hour of the onset of symptoms.¹⁴ In men he found an incidence of 0.1 to 1.7 per 1000 under 50 years, of 1.7 to 6.4 from 50-69 years, and of 13.1 to 19.5 over 69 years. For women the corresponding figures were 0.1 to 0.2, 0.4 to 2.0, 1.5 to 7.1. In the Framingham-Albany study of men the incidence per 1000 was 1.2, 3.9, and 3.0 respectively in age groups 45-54, 55-64, and 65-74.¹⁵ This differs from Romo's findings and from our own as regards the oldest age group. The difference is difficult to explain, but in the Framingham-Albany study only 10 deaths in this age group were recorded.

One approach to prevention of sudden cardiac death may be to identify and treat subjects at greatest risk. In this study 75% of all patients who died of sudden cardiac death had manifest ischaemic heart disease or hypertension. A similar proportion was found in Baltimore³ but a lower one in other studies.^{1,16} In the present study ischaemic heart disease was not recorded in 70% of all patients with sudden cardiac death under 50 years of age and in 45% between 50 and 69 years of age (Fig. 1). Table 4 shows the estimated prevalence of ischaemic heart disease, defined as previous acute myocardial infarction or existing angina pectoris, in the Danish population. The estimate is based on other Danish population studies.¹⁷⁻¹⁹ On the basis of these figures is calculated the incidence of sudden cardiac death in subjects with and without ischaemic heart disease. Among younger subjects sudden cardiac death occurs mainly in those without known ischaemic heart disease, whereas in middle aged men an equal number occurs in men with

Table 4 Estimated prevalence of ischaemic heart disease (IHD), defined as previous acute myocardial infarction or angina pectoris, in a Danish population¹⁷⁻¹⁹ and estimated incidence of sudden cardiac death (SCD) in subjects with and without ischaemic heart disease

Age group (yr)	Incidence of SCD (per 1000 population)	Estimated values (rate per 1000 population)		
		Prevalence of IHD	Incidence of SCD in subjects	
			With IHD	Without IHD
Men				
<50	0.019	1.3	7.5	0.095
50-69	0.36	10.0	19.3	1.8
≥70	1.14	13.0	73.5	2.3
Women				
<50	0.012	1.0	—	0.13
50-69	0.10	2.0	28.6	0.43
≥70	0.64	10.0	45.0	2.4

and without known ischaemic heart disease. In middle aged women and elderly men and women most sudden cardiac deaths occur in subjects with known ischaemic heart disease. Overall, most sudden cardiac deaths occur in subjects with known ischaemic heart disease. If effective prevention programmes were possible, the most immediate effect could be on the total number of sudden cardiac deaths in programmes applied to subjects with existing ischaemic heart disease.

The recorded incidence of prodromes before sudden cardiac death depends on the method of investigation. In our study 38% of cases were reported to have had prodromes, but this included only information available from doctors, police reports, etc—that is, only of prodromes so severe that they had been reported before death or that the relatives had disclosed after death. In contrast, Alonzo *et al.* interviewed the relatives after death and found that 64% of victims had complained of prodromes.¹⁶ In our study, in 28% of all cases of sudden cardiac death the victims had consulted a doctor in the two weeks before death; this figure is slightly lower than in other studies, in which the proportion was 36–38%.^{3,14,16}

More of the patients with known ischaemic heart disease or hypertension had consulted a doctor recently, 32% within two weeks and 61% within two months (Fig. 3b), compared with 51% in the study of Alonzo *et al.*¹⁶ Prodromes were very frequent in this group especially among patients with angina pectoris. Of patients without ischaemic heart disease or hypertension, 14% had consulted a doctor in the two weeks before death (Fig. 3b), a similar proportion to that found by Alonzo *et al.*¹⁶ Twenty four patients had prodromes that retrospectively were found to be cardiac in origin, but no action had been taken because of them. Thirty two patients (19% of all cases of sudden cardiac death) could not have been identified as being at risk for sudden cardiac death by detecting pre-existing ischaemic heart disease or hypertension or by the presence of cardiac prodromes.

Non-acute myocardial infarction episodes are reported to be associated with an increased risk of cardiac death.⁶⁷ In our study, in the 166 cases of sudden cardiac death, only 14 (8%) patients had non-acute myocardial infarction episodes less than two years before death, which is a very small proportion (Fig. 4) but comparable to the figure of 15 (9%) who had suffered from acute myocardial infarction over a similar period. Prophylaxis in this group may therefore be almost as important as in patients after acute myocardial infarction.

In only 13 patients had an acute myocardial infarction occurred less than one year before death, which is the period often recommended for medical prophylaxis after acute myocardial infarction (Fig. 4). Eleven of these 13 had angina pectoris or hypertension—possible indications for beta blocker treatment—and five were already receiving beta blockers (Table 3). At the time of the study none of the hospitals in the region gave beta blockers prophylactically to patients with acute myocardial infarction. Thus if acute myocardial infarction patients with hypertension or angina pectoris are treated with beta blockers or any other drug with a possible prophylactic effect on sudden cardiac death only very few cases of sudden cardiac death could possibly be prevented. Furthermore the impact of sudden cardiac death in society would hardly be influenced even by the use of routine prophylactic treatment after acute myocardial infarction since only 8% of sudden cardiac death victims had acute myocardial infarction less than one year before death.

Financial support was received from the Danish Heart Foundation, August Frederik Wedell Erichsens Legat, Arvid Nilssons Fond, and the Foundation for Medical Research of Bornholm, Frederiksborg, Roskilde, Storstrøm, and Vestsjælland counties.

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Benign coronary perforation during percutaneous transluminal coronary angioplasty

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SUMMARY In two patients percutaneous transluminal coronary angioplasty was complicated by coronary perforation. In both cases the complication was managed conservatively.

Two cases of coronary perforation or rupture during percutaneous transluminal coronary angioplasty have been reported. One patient was successfully treated with pericardiocentesis and emergency bypass surgery¹ and the other died despite pericardiocentesis.² We report two cases of coronary artery perforation during angioplasty that resolved spontaneously.

Patients and methods

CASE 1

A 58 year old man was admitted for repeat percutaneous transluminal coronary angioplasty five months after successful angioplasty of a stenosis of the right coronary artery. He had been free of symptoms for about two months after his initial treatment. Two weeks before repeat angioplasty a control coronary angiogram showed recurrence of the dilated stenosis (Fig. 1a). The patient was taking a regimen of aspirin 100 mg daily, nitrates, and calcium antagonists. After the intravenous administration of 10 000 U heparin and intracoronary administration of 0.1 mg nifedipine and 0.2 mg isosorbide dinitrate a steerable guide wire (Schneider 0.014 inch) could be advanced with difficulty 2 cm past the stenosis where further advancement became impossible. An injection of contrast medium through the catheter tip already beyond the stenosis failed to opacify the distal vessels but resulted in a linear deposit of contrast outlining the inferior pericardial sac (Fig. 1b). The balloon catheter and guide wire were withdrawn proximal to the stenosis. The patient remained haemodynamically stable and free of pain. The guide wire was advanced again, this time deep into a left ventricular branch. The balloon catheter could be advanced easily and a

distal injection of contrast outlined the artery containing the guide wire. Several dilatations up to 8 atmospheres were performed with a pronounced reduction of the stenosis evidenced by control angiography, which showed no further extravasation. Remnants of the pericardial deposit of contrast were still visible (Fig. 1c). The effects of the heparin were not reversed, and the patient was discharged two days later after an uneventful recovery. Eight months later, when the patient was seen as an outpatient, he was free of symptoms.

CASE 2

A 60 year old man was admitted to hospital for unstable angina. Cardiac catheterisation showed a normal left ventricle and two moderate stenoses of the left anterior descending coronary artery after the junction with a diagonal branch, which was totally occluded but faintly collateralised (Fig. 2a). The left circumflex coronary artery showed a non-significant narrowing, and the right coronary artery was normal. The patient's angina remained unstable requiring treatment in the coronary care unit. Five days later percutaneous transluminal coronary angioplasty was performed. After a pretreatment regimen identical to that in case 1 a Schneider 3.0 mm balloon catheter was advanced over a guide wire (Schneider 0.014 inch), which had been manoeuvred with difficulty across the total occlusion of the diagonal branch. A distal injection of contrast medium opacified the distal portion of the diagonal branch. Several dilatations up to 6 atmospheres were performed. Distal pressure rose from 35 mm Hg to 75 mm Hg. A control injection showed patency of the formerly occluded segment but also extravasation of contrast medium. The patient complained of a dull chest pain but remained haemodynamically stable. The balloon catheter was withdrawn, and angioplasty of the two stenoses in the left anterior descending coronary artery was successfully performed. A final injection of contrast showed

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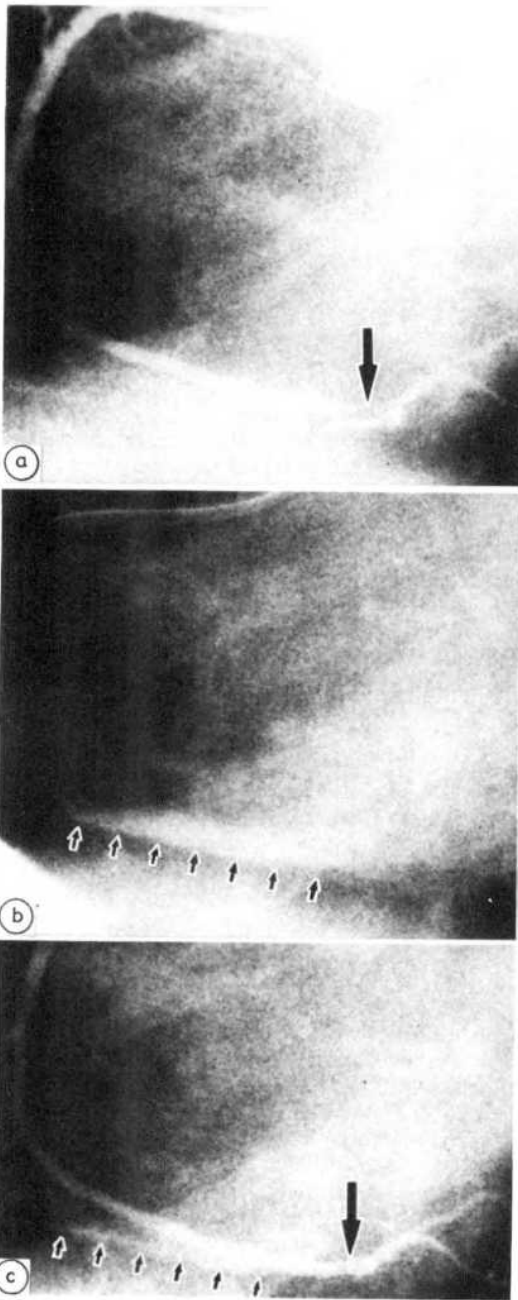


Fig. 1 Case 1: Coronary angiograms showing the right coronary artery in the left anterior oblique projection (a) before angioplasty (stenosis indicated by large arrow); (b) after perforation (contrast deposit is visible in the pericardial sac (small arrows); and (c) after angioplasty (dilated segment indicated by large arrow, remnants of pericardial contrast deposit by small arrows).

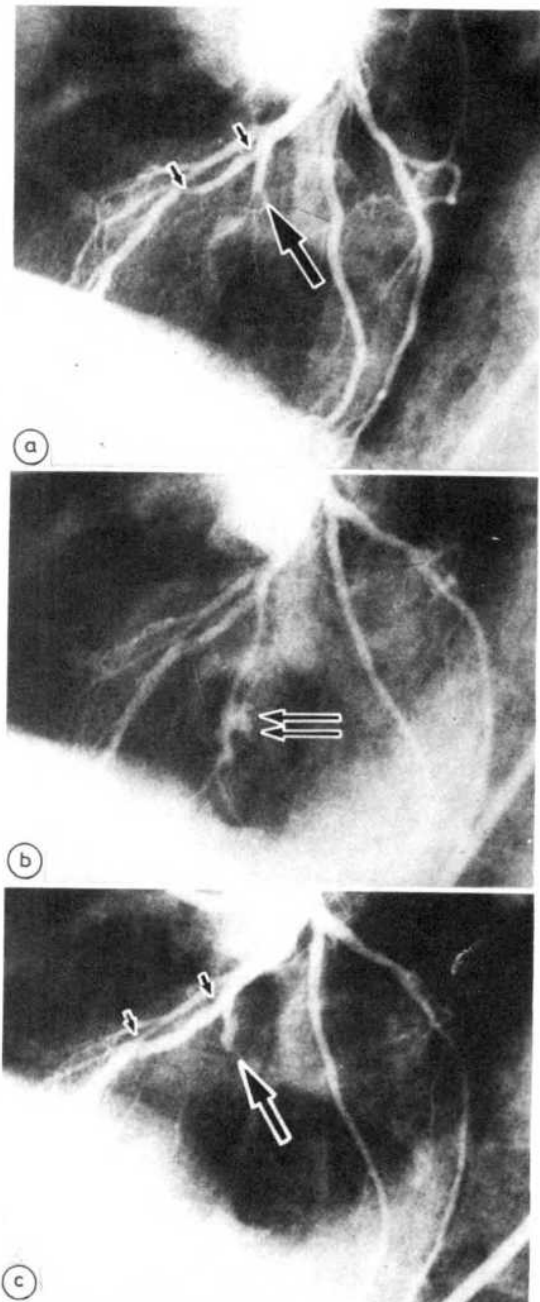


Fig. 2 Case 2: Coronary angiograms showing the left coronary artery in the left anterior oblique projection with cranial angulation (a) before angioplasty (stenosis of left anterior descending coronary artery indicated by small arrows, occlusion of diagonal branch indicated by large arrow), (b) after angioplasty (contrast extravasation indicated by double arrow), and (c) two weeks later (site of previous stenoses of left anterior descending coronary artery indicated by small arrows, reocclusion of diagonal branch indicated by large arrow).

continuing extravasation of contrast medium at the site of the previous occlusion of the diagonal branch and patency of the vessel itself (Fig. 2b). The contrast deposit around the dilated vessel drained slowly into the pericardium. The effects of heparin were reversed with protamine sulphate, and an intravenous glyceryl trinitrate infusion was continued. Chest pain persisted for about two hours. No haemodynamic alteration, pericardial rub, increase in creatine phosphokinase activity, or electrocardiographic changes were observed. A few days later the patient complained again about exertional angina. Control coronary angiography two weeks after angioplasty showed reocclusion of the diagonal branch at the initial site. The left anterior descending coronary artery was widely patent (Fig. 2c). Repeat angioplasty of the occluded diagonal branch was not attempted, and conservative treatment was recommended. Eight months later the patient was free of symptoms with a regimen consisting of a calcium blocker, nitrates, and aspirin.

Discussion

Our first case represents perforation of a distal coronary artery with the guide wire and the tip of the balloon catheter. Recognition of the false passage before balloon dilatation prevented enlargement of the perforation and allowed spontaneous sealing. This case emphasises the importance of a distal injection of contrast before balloon filling to determine the correct intraluminal position of the balloon catheter.

Our second case represents a rupture of a relatively small branch as a result of the dilatation process itself.

It is conceivable that both guide wire and balloon catheter were advanced subintimally through the occlusion re-entering the correct lumen distal to it. The correct intraluminal position of the balloon tip before balloon filling was established both by pressure measurement and dye injection. Dilatation with the relatively large balloon resulted in transmural dissection of the arterial wall. Rapid termination of the angioplasty procedure with prompt reversal of heparinisation was probably crucial in preventing cardiac tamponade. Unfortunately, not only the perforation but also the re-established lumen closed spontaneously. The patient, however, still benefited from the successful angioplasty of the strategically more important lesions in the left anterior descending coronary artery.

Drastic measures such as reocclusion of the bleeding vessel with the balloon, pericardiocentesis, or emergency operation suggested or performed in previously reported cases of coronary perforation^{1,2} were not necessary in these patients. Thus coronary perforation due to balloon angioplasty may resolve spontaneously but still demands careful supervision and readiness for active treatment.

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Milrinone in heart failure

Acute effects on left ventricular systolic function and myocardial metabolism

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SUMMARY Milrinone, a new bipyridine compound related to amrinone, is a potent non-adrenergic inotrope in experimental preparations and also shows vasodilator activity. In the present study the haemodynamic and metabolic effects of milrinone were evaluated in 12 patients with congestive heart failure. Milrinone 5 mg given orally produced a sharp reduction in left ventricular end diastolic pressure without significantly affecting stroke volume. The improvement in left ventricular function was due to a combination of vasodilatation and positive inotropism. Thus small reductions in blood pressure and systemic vascular resistance were associated with increments in the isovolumic indices of left ventricular function. The relation between left ventricular end systolic pressure and dimension was displaced leftwards and downwards. Only reductions in left ventricular cavity dimension were statistically significant, however. Though myocardial oxygen consumption did not change significantly, it tended to increase whereas lactate consumption tended to decrease.

This trend towards oxygen imbalance suggests the need for caution in the use of milrinone in patients with severe coronary artery disease.

Milrinone is a recently introduced derivative of amrinone. Both compounds share a bipyridine ring structure and increase the contractility of isolated heart muscle.¹ The inotropic potency of milrinone, however, is 10-30 times greater than that of its parent compound.² The mechanism of this inotropic effect remains unclear. Milrinone is a potent inhibitor of cyclic adenosine monophosphate adenylic acid (AMP) phosphodiesterase,¹ but peak increments in muscle tension precede maximal increase in intracellular cyclic AMP.² Phosphodiesterase inhibition is unlikely, therefore, to account fully for the inotropic properties of the drug. In addition to its direct cardiac effects, milrinone also relaxes vascular smooth muscle in experimental preparations, though at considerably higher doses than are required to produce a positive inotropic response.²

Recent work has confirmed beneficial haemo-

dynamic responses to milrinone in patients with congestive heart failure.³⁻⁵ The contributions that positive inotropism and vasodilatation make towards the clinical efficacy of the drug are, however, unknown. This question is important because the balance of these separate cardiovascular influences largely determines the effects of treatment on myocardial oxygen demand—a consideration of particular relevance in patients with coronary artery disease.⁶

In the present study, therefore, we measured haemodynamic and metabolic responses to milrinone in patients with congestive heart failure. In particular, we evaluated the effects of this agent on left ventricular systolic function—as determined by contractile performance and loading conditions—and myocardial oxygen consumption.

Patients and methods

PATIENT SELECTION

Twelve patients (10 men, two women; age range 31-64 (mean) 52.7 years) were studied (Table 1). All

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Accepted for publication 19 March 1985

Table 1 Patient characteristics

Case No	Sex/age (yr)	Diagnosis	NYHA class	EF (%)	LVEDP (mm Hg)	Daily furosemide dosage (mg)
1	M/39	CAD	III	10	31	120
2	M/55	CAD	III	27	16	250
3	M/45	CAD	II	44	24	80
4	M/54	CAD	III	13	23	80
5	M/64	CAD	III	NA	17	80
6	M/58	CCM	III	19	28	240
7	F/50	CCM	II	39	8	40
8	M/31	CCM	III	22	14	40
9	M/60	CAD	III	21	24	80
10	F/59	CCM	III	NA	25	160
11	M/53	CCM	III	23	8	120
12	M/64	CAD	III	10	15	120

CAD, coronary artery disease; CCM, congestive cardiomyopathy, EF, angiographic ejection fraction (not available (NA) in two cases), LVEDP, left ventricular end diastolic pressure (measured in the supine position).

were selected on the basis of moderate to severe congestive heart failure (New York Heart Association functional classes II and III) that had responded inadequately to conventional treatment. Ten patients had undergone diagnostic cardiac catheterisation within 12 months of the study. This had confirmed severely impaired left ventricular function with a mean (SEM) angiographic ejection fraction of only 23 (4)%. Seven of the 10 patients had coronary artery disease by angiographic or clinical criteria and the remainder congestive cardiomyopathy of uncertain cause. The patients were all in stable sinus rhythm. Written informed consent was obtained from each patient before inclusion in the study, which had been approved by the hospital ethical committee.

CARDIAC CATHETERISATION

The patients were studied in the supine position after fasting. Premedication with diazepam 5–10 mg orally was given. Heparin 1000 IU/hour was administered by continuous intravenous infusion for 12 hours before and during each study. All catheterisation procedures were performed under fluoroscopic control using up to 20 mg of lignocaine local anaesthetic. A balloon tipped triple lumen thermodilution catheter (Edwards Laboratories Inc) was placed in the pulmonary artery. This permitted technically adequate right sided pressure measurements in all the patients except one, in whom baseline error made data interpretation impossible. In a second patient a satisfactory pulmonary capillary wedge pressure recording could not be obtained. The mean of at least four thermodilution cardiac output recordings was taken for each measure of cardiac output. Arterial pressure was monitored, and blood samples obtained, through the sidearm of a short sheath positioned in the femoral artery. A micromanometer tipped catheter (Millar Instruments Inc) was introduced through the femoral arterial sheath and positioned in the left ventricle for high fidelity pressure recordings. All pressures were measured

with reference to the mid-chest and were recorded with an electrocardiogram on a Mingograph 82 recorder (Siemens Ltd). Coronary sinus cannulation with a dual thermistor catheter (Wilton Webster Ltd) was performed in 10 patients using the techniques described by Ganz *et al.*⁷ This permitted determination of coronary sinus flow by continuous thermodilution. Adequate coronary sinus blood sampling for metabolic measurements was possible in eight of these patients.

ECHOCARDIOGRAPHY

In seven patients M mode echocardiograms (Hewlett Packard phased array sector scanner) of the left ventricular cavity were obtained at a level just below the free margins of the mitral valve leaflets where the septum and posterior wall were clearly visible. These images were recorded simultaneously with the left ventricular pressure signal at a paper speed of 100 mm/s. During these recordings the atrium was paced at a fixed preselected rate (15–20 beats/minute in excess of the control heart rate). The isovolumic indices of left ventricular function were also measured during fixed rate atrial pacing.

DRUG ASSAY

Serum samples for estimating milrinone concentrations were obtained in seven patients. A high pressure liquid chromatographic assay was used and was performed at the Sterling-Winthrop Research Centre.

STUDY PROTOCOL

Vasodilator drugs were withdrawn four days before the study. All other regular medications were withheld on the morning of the study. After placement of the catheters the patients were permitted to rest for 15 minutes, and two sets of control haemodynamic measurements were then obtained 20 minutes apart. At the same time blood samples were withdrawn from the coronary sinus and the femoral artery for later

Table 2 Haemodynamic responses to milrinone in 12 patients with congestive heart failure. Values are mean (SEM)

	Before milrinone 5 mg (min)		After milrinone 5 mg (min)			p value†
	20	0	30	60	90	
Heart rate (beats/min)	84 (5)	84 (5)	87 (5)	90 (5)*	89 (5)	<0.01
Cardiac index (l/min per m ²)	2.4 (0.2)	2.4 (0.1)	2.5 (0.1)	2.7 (0.1)**	2.7 (0.2)*	<0.001
Stroke volume index (ml/beat per m ²)	29 (2)	29 (2)	30 (1)	31 (2)	31 (2)	NS
Systolic blood pressure (mm Hg)	139 (7)	141 (7)	136 (7)	134 (7)	130 (7)**	<0.01
Diastolic blood pressure (mm Hg)	82 (2)	81 (3)	79 (3)	77 (3)	78 (3)	<0.05
Mean blood pressure (mm Hg)	101 (4)	102 (4)	97 (4)	94 (4)*	95 (5)*	<0.01
Systemic vascular resistance (units)	23 (1)	23 (1)	20 (1)	18 (1)***	19 (2)**	<0.001
Mean right atrial pressure (mm Hg) (n=11)	10 (2)	10 (2)	8 (2)*	7 (2)***	8 (2)*	<0.001
Mean pulmonary artery pressure (mm Hg) (n=11)	30 (3)	29 (3)	23 (3)**	22 (3)***	23 (3)***	<0.001
Pulmonary capillary wedge pressure (mm Hg) (n=10)	21 (2)	21 (2)	13 (2)***	10 (2)***	10 (2)***	<0.001
Left ventricular end diastolic pressure (mm Hg)	19 (2)	20 (2)	13 (2)**	9 (2)***	8 (2)***	<0.001
Left ventricular max dP/dt (mm Hg/s)	1160 (124)	1167 (119)	1278 (150)	1283 (150)*	1228 (124)	<0.01
Left ventricular max dP/dt/P (s ⁻¹)	22 (2)	22 (2)	31 (3)***	37 (3)***	35 (3)***	<0.001
Left ventricular min dP/dt (mm Hg/s)	-1096 (54)	-1091 (50)	-1237 (97)*	-1238 (91)*	-1250 (88)**	<0.01
Coronary sinus flow (ml/min) (n=10)	108 (12)	106 (12)	113 (14)	125 (21)	136 (25)	NS
Coronary resistance (units) (n=10)	0.96 (0.11)	0.98 (0.11)	0.92 (0.13)	0.86 (0.13)	0.83 (0.13)	NS

†Overall significance of changes by analysis of variance, NS, not significant; significance of individual changes with respect to second set of control readings (at 0 min): *p<0.05, **p<0.01, ***p<0.001.

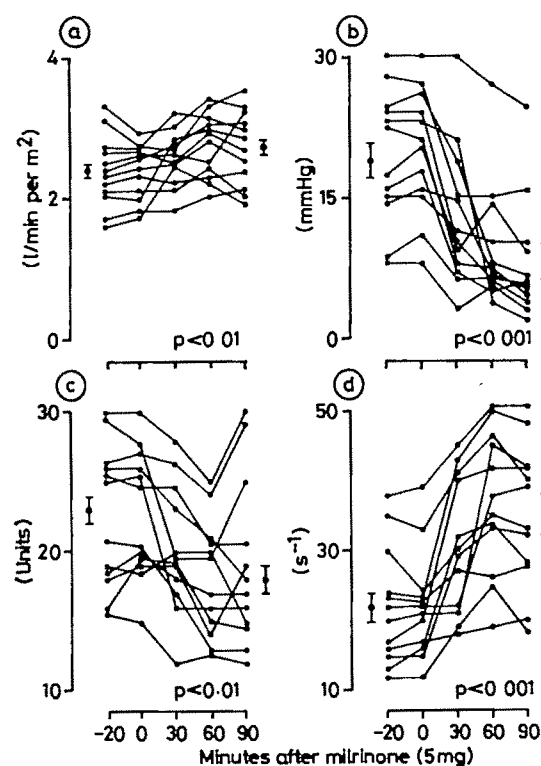


Fig. 1 Effects of milrinone on (a) cardiac index, (b) left ventricular end diastolic pressure, (c) systemic vascular resistance, and (d) left ventricular maximum dP/dt/P in 12 patients. Mean (SEM) values are shown at baseline and 90 minutes after milrinone.

biochemical analysis. Milrinone 5 mg was given orally, and haemodynamic measurements and blood sampling were repeated 30, 60, and 90 minutes later. The simultaneous left ventricular echocardiogram and pressure recordings were obtained at the same time intervals but always after the other haemodynamic variables had been measured and the blood samples had been taken.

DATA ANALYSIS

Measurements of stroke volume and vascular resistance (expressed in arbitrary units) were derived by standard formulae. Cardiac output and stroke volume were normalised for body surface area. Isovolumic indices of left ventricular function—the rate of rise of pressure (dP/dt) and the quotient of dP/dt and instantaneous pressure (P)—were derived by simultaneous analogue processing of the left ventricular pressure signal. The simultaneous records of left ventricular pressure and septal and posterior wall endocardial echoes were digitised between two consecutive R waves on the electrocardiogram using a high resolution (0.1 mm) digitising tablet (Summagraphics Ltd) interfaced with a microcomputer system (Commodore).

Arterial and coronary sinus blood samples were assayed for whole blood lactate.⁸ Whole blood oxygen and haemoglobin concentrations were measured using a Radiometer OSM2 Hemoximeter; oxygen content was derived by the standard formula. Arterio-coronary sinus concentration differences in whole blood were calculated and the myocardial extraction ratios derived by dividing the arterio-coronary sinus differences by the arterial concentrations expressed as a

Table 3 Serum milrinone concentrations. Values are mean (SEM) (n=7)

	Before milrinone 5 mg (min)		After milrinone 5 mg (min)		
	20	0	30	60	90
Serum milrinone concentration (ng/ml)	ND	ND	89.3 (37.3)	123.9 (25.8)	102.5 (13.2)

ND, not detectable

percentage. Myocardial uptake was calculated as the product of arteriocardiac sinus concentration difference in whole blood and coronary sinus flow.

STATISTICAL ANALYSIS

Two way analysis of variance was used to test the significance of the overall changes in individual haemodynamic and metabolic variables across time. Those variables which changed significantly ($p < 0.05$) were then subjected to a modified *t* test—using the Bonferroni method—to identify the source of the differences.⁹

Results

No drug related side effects occurred during the study.

HAEMODYNAMIC RESPONSES

Table 2 summarises the haemodynamic responses to milrinone and Fig. 1 shows the individual patient data. Table 3 gives the serum milrinone concentrations.

The data in Tables 1 and 2 confirm the severe

baseline left ventricular impairment that characterised this group of patients. Angiographic ejection fraction was depressed, and despite treatment with frusemide both the left ventricular end diastolic pressure and the echocardiographic cavity dimensions were considerably increased (Fig. 2). Cardiac index and stroke volume index, on the other hand, showed variable reductions below the normal range.

Although milrinone produced a prompt reduction in the increased left ventricular filling pressures (as reflected by the changes in left ventricular end diastolic pressure and pulmonary capillary wedge pressure) and a small reduction in right atrial pressure, cardiac index was increased. Stroke volume index, however, did not change significantly because of a small increase in heart rate. Reductions in blood pressure and systemic vascular resistance, though significant, were not pronounced. The isovolumic indices of left ventricular systolic function (max dP/dt and max dP/dt/P) both increased, the rise in max dP/dt/P being particularly prominent. A tendency for coronary sinus flow to increase and for coronary resistance to decline was not significant.

Milrinone produced a leftward shift in the relation

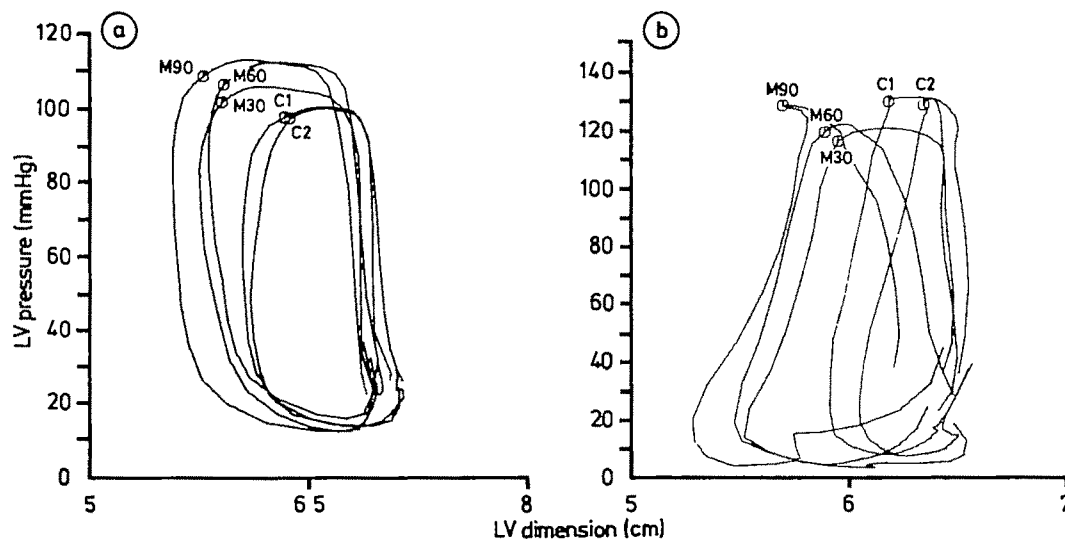


Fig. 2 (a) and (b). Effects of milrinone on the relation between left ventricular (LV) pressure and dimension in two separate patients. Values before treatment (C1 and C2) and 30, 60, and 90 minutes after milrinone (M30, M60, M90) are shown. Open circles indicate the pressure-dimension relation at end systole.

Table 4 Changes in left ventricular end systolic pressure and dimension. Values are mean (SEM) (n=7)

Left ventricular end systolic values	Before milrinone 5 mg (min)		After milrinone 5 mg (min)			p value†
	20	0	30	60	90	
Pressure (mm Hg)	109 (5)	108 (5)	105 (6)	102 (5)	105 (6)	NS
Dimension (cm)	6.3 (0.3)	6.3 (0.3)	6.0 (0.3)*	5.9 (0.3)**	5.8 (0.3)**	<0.001

†Overall significance of changes by analysis of variance. NS, not significant; significance of individual changes with respect to second set of control readings (at 0 min): *p<0.05, **p<0.01.

between end systolic pressure and dimension (Fig. 2). The reduction in dimension was significant and was slightly more pronounced than the reduction in pressure (Table 4). In one patient reduction in the left ventricular end systolic cavity dimension occurred during a progressive increase in pressure (Fig. 2a). More commonly, however, small reductions in end systolic pressure were observed (Fig. 2b).

METABOLIC RESPONSES

Table 5 summarises the effects of milrinone on oxygen and lactate metabolism. Arterial oxygen saturation and myocardial oxygen extraction remained remarkably constant during the study. Myocardial oxygen uptake, however, tended to increase though the trend was not statistically significant. The arterial concentration of lactate was also unaffected by milrinone, but the myocardial utilisation of this substrate declined; the fall in lactate extraction was significant. No patients showed lactate production during this study.

Discussion

This study has shown that the acute administration of milrinone to patients with heart failure is well tolerated and leads to a useful improvement in resting left ventricular function. The data indicate that positive inotropism and vasodilatation combine to produce this beneficial effect.

The patients included in this study all had moderate to severe degrees of heart failure caused by coro-

nary artery disease or congestive cardiomyopathy. Milrinone produced only a small improvement in cardiac output, but the left ventricular filling pressures fell and in most patients were within the normal range 60–90 minutes after drug administration. This reduction in filling pressures during maintenance of cardiac output must reflect an improvement in left ventricular function.

In studies of this type analysis of the mechanisms responsible for changes in left ventricular function is difficult. The effects of milrinone on the isovolumic indices of left ventricular performance and the relation between end systolic pressure and dimension, however, strongly suggest a positive inotropic response to the drug. The isovolumic indices of ventricular performance provide a measure of contractile function but are also influenced by heart rate and loading conditions.^{10,11} In the present study the changes in loading that occurred in response to milrinone would have tended to reduce left ventricular max dP/dt.¹⁰ Because atrial pacing controlled for changes in heart rate, the increase in left ventricular max dP/dt during the study is best explained by an increase in contractility. Left ventricular max dP/dt/P is less susceptible to the influence of loading conditions,¹¹ and the drug induced improvement in this measure of contractile function strengthens the conclusion that positive inotropism contributed towards the beneficial effects of milrinone.

The leftward displacement of the relation between left ventricular end systolic pressure and dimension that occurred in response to milrinone was due to a

Table 5 Metabolic responses to milrinone in eight patients with congestive heart failure. Values are mean (SEM)

	Before milrinone 5 mg (min)		After milrinone 5 mg (min)			p value†
	20	0	30	60	90	
Oxygen.						
Arterial saturation (%)	96.4 (0.5)	96.5 (0.9)	97.0 (0.8)	96.4 (0.8)	95.0 (0.9)	NS
Myocardial extraction (%)	64.7 (2.0)	63.3 (2.5)	63.8 (2.5)	63.8 (2.4)	63.3 (2.2)	NS
Myocardial uptake (ml/min)	13.9 (2.0)	13.3 (1.7)	14.5 (2.4)	16.0 (3.2)	18.2 (4.1)	NS
Lactate.						
Arterial concentration (mmol/l)	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	NS
Myocardial extraction (%)	29.5 (5.2)	29.7 (5.4)	23.5 (6.9)	21.9 (6.5)	16.4 (5.3)***	<0.001
Myocardial uptake (μmol/min)	35.0 (7.0)	33.9 (6.8)	30.8 (10.4)	34.1 (12.5)	25.9 (9.1)	NS

†Overall significance of changes by analysis of variance. NS, not significant; significance of individual changes with respect to second set of control readings (at 0 min): ***p<0.001.

significant reduction in cavity dimension. The reduction in end systolic pressure was not significant (unlike the change in peak systolic pressure measured in larger numbers of patients). Indeed in one case left ventricular pressure increased during simultaneous reductions in cavity dimension. Though we have previously emphasised the caution that is necessary in interpreting data of this type¹² (extrapolation from pressure-volume relations in the normal heart to pressure-dimension relations in the failing heart has not, as yet, been validated experimentally¹³) the reduction in end systolic dimension without pronounced alteration in end systolic pressure suggests a positive inotropic response to the drug.¹⁴ The response to milrinone should be contrasted with the response to felodipine—a potent vasodilator—which produces a pronounced downward displacement in the relation between the end systolic pressure and dimension in patients with heart failure.¹²

The useful reduction in left ventricular filling pressures that occurred during this study is explained in part by the effects of milrinone on diastolic ventricular function. Preliminary work has shown that this drug improves indices of left ventricular diastolic relaxation and chamber distensibility in patients with heart failure.¹⁵ Our finding of a significant increase in left ventricular min dP/dt supports this observation. Associated systemic venous pooling, however, is likely to have contributed to the reduction in ventricular filling pressures, and the small reductions in blood pressure and systemic vascular resistance point to associated arteriolar dilatation. Vasodilatation, therefore, appears to make an important contribution to the beneficial haemodynamic effects of milrinone as indicated by the data of Cody *et al.*¹⁶

The metabolic consequence of antifailure treatment is an important consideration in the assessment of new agents. Milrinone produced a small increase in heart rate in addition to enhancing contractility. Increments in myocardial oxygen demand, however, were to some extent offset by associated reductions in wall tension caused by diminished left ventricular cavity dimensions and vasodilatation.¹⁷ Thus myocardial oxygen consumption and lactate production did not change significantly. Both variables, however, tended to increase and the associated rise in myocardial lactate extraction was statistically significant. Though the determinants of lactate extraction are complex,¹⁸ our data do not exclude an adverse effect on myocardial ischaemia: further work is necessary to evaluate this issue.

The beneficial haemodynamic effects of milrinone in congestive heart failure are confirmed in the present study. The drug, which is well tolerated, improves left ventricular systolic function as a result of simultaneous positive inotropism and vasodilata-

tion. The combination of these separate cardiovascular influences to some extent protects against myocardial ischaemia. The changes that occurred in oxygen and lactate metabolism, however, although not statistically significant, suggest the need for caution in the use of milrinone in patients with severe coronary artery disease.

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Milrinone in heart failure

Effects on exercise haemodynamics during short term treatment

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SUMMARY The effects of milrinone, a new bipyridine inotropic agent, on the haemodynamic responses to treadmill exercise were studied in 12 patients with congestive heart failure. Four weeks' treatment with milrinone 20 mg daily produced an improvement in left ventricular function during exercise as reflected by significant increments in cardiac index and stroke volume index without change in pulmonary capillary wedge pressure. Systemic oxygen consumption, measured at sub-maximal exercise, also increased suggesting that the drug induced rise in stroke output was associated with improved skeletal muscle perfusion. Maximum exercise capacity increased. Importantly, the beneficial effects of milrinone on exercise haemodynamics and exercise tolerance were sustained throughout the four week treatment period. No drug related side effects occurred. After treatment with milrinone was stopped left ventricular function deteriorated to a level slightly, but significantly, worse than that before treatment.

These observations indicate a potentially useful role for milrinone in treating heart failure.

Although treatment with diuretics effectively controls the congestive manifestations of heart failure, the search for agents that provide sustained improvement in left ventricular function has been disappointing. The value of digitalis remains controversial,¹ and despite the beneficial acute effects of vasodilators and beta adrenoceptor stimulants attenuation of responsiveness to these agents frequently occurs.²⁻⁴ The introduction of amrinone, therefore (a non-adrenergic inotropic agent) generated considerable interest. Amrinone is a bipyridine compound that improves left ventricular function in the short term,^{5,6} though long term benefit has not been confirmed in controlled studies.⁷ The clinical usefulness of amrinone is further limited by its toxic properties, which have led to thrombocytopenia and gastrointestinal intolerance in many patients treated with the drug.⁸ More recently, a second bipyridine compound, milrinone, has been developed. Milrinone has greater positive inotropic potency than amrinone in experimental pre-

parations⁹ and, importantly, does not appear to share the toxic properties of its parent compound.¹⁰⁻¹² In patients with heart failure, milrinone produces a prompt improvement in left ventricular function through a combination of positive inotropism and vasodilatation; long term benefit in terms of improved exercise tolerance has also been reported.¹⁰⁻¹² Placebo treatment, however, can have similar beneficial effects on exercise tolerance in heart failure,¹³ and for this reason measurement of the haemodynamic responses to exercise is necessary to confirm sustained drug efficacy. In this report we describe the effects of milrinone on haemodynamic responses to treadmill exercise during treatment of patients with congestive heart failure.

Patients and methods

PATIENT SELECTION

The 12 patients included in this short term evaluation of milrinone had all undergone an acute haemodynamic study with the same drug at least three days previously (range 3-16 days). Table 1 summarises the patients' characteristics and selection criteria, which have been previously described.¹⁴ Written

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Accepted for publication 19 March 1985

Table 1 Patient characteristics

Case No	Sex/age (yr)	Diagnosis	NYHA class	EF (%)	LVEDP (mm Hg)	Daily furosemide dosage (mg)
1	M/39	CAD	III	10	31	120
2	M/55	CAD	III	27	16	250
3	M/45	CAD	II	44	24	80
4	M/54	CAD	III	13	23	80
5	M/64	CAD	III	NA	17	80
6	M/58	CCM	III	19	28	240
7	F/50	CCM	II	39	8	40
8	M/31	CCM	III	22	14	40
9	M/60	CAD	III	21	24	80
10	F/59	CCM	III	NA	25	160
11	M/53	CCM	III	23	8	120
12	M/64	CAD	III	10	15	120

CAD, coronary artery disease; CCM, congestive cardiomyopathy; EF, angiographic ejection fraction (not available (NA) in two cases); LVEDP, left ventricular end diastolic pressure (measured in the supine position)

informed consent was obtained from each patient before inclusion in the study, which had been approved by the hospital ethical committee.

STUDY PROTOCOL

All vasodilator treatment was discontinued at least a week before the study. Digoxin (four patients) and diuretic treatment were continued throughout the 30 days of the study without alteration in dosage. Exercise studies were always performed after fasting late in the afternoon about four to five hours after the mid-day milrinone capsule. The daily dose of diuretics and other regular medications were not withheld. The protocol was for a total of five exercise tests in each patient. The first, a preliminary test, permitted an assessment of maximal exercise capacity and was performed without invasive haemodynamic measurements. On day 1 of the study control haemodynamic data during exercise were obtained, after which treatment with oral milrinone 20 mg daily divided into four doses was started. Further exercise tests were performed after two days and four weeks' of treatment—days 3 and 28 respectively. After day 28 milrinone was withdrawn, and two days later (day 30) the final exercise test was performed. Ten patients completed the protocol. One patient was withdrawn from the study after day 3 because of a transient cerebral ischaemic attack, which was not thought to be drug related. Another patient did not undergo the final exercise test after drug withdrawal on day 30.

The patients were treated in hospital for the first three days of the study, after which outpatient follow up, with weekly review, continued until the last three days of the study when they were readmitted. At each follow up visit inquiries were made about drug related side effects, and the patients were supplied with 28 milrinone capsules (one week's supply). Compliance was confirmed by capsule counting. Blood samples for platelet estimation were obtained before exposure to milrinone and again after four weeks treatment (day 28).

EXERCISE TESTS

Heart rate was monitored from a precordial lead. Arterial blood pressure was recorded from a cannula placed in the radial artery. A balloon tipped thermodilution catheter placed in the pulmonary artery was used to monitor pulmonary capillary wedge pressure and cardiac output (measured in duplicate using 10 ml of iced saline). All pressures were measured in the upright posture with reference to the sternal angle. This underestimated true left atrial pressure but ensured a constant zero level for all exercise tests. Arterial and mixed venous samples for gas analysis were drawn from the radial artery and the pulmonary artery respectively within one minute of the cardiac output measurements. Blood oxygen content, arteriovenous oxygen difference, systemic oxygen consumption index, and derived haemodynamic variables were calculated using standard formulae.

All patients were exercised on a treadmill. The Bruce protocol was used in seven cases but in the remainder, all of whom were more severely symptomatic, the less demanding Naughton protocol was used. The same exercise protocol was used throughout the study in individual patients. After maximal exercise capacity had been established in the preliminary test an arbitrary 70–80% submaximal level was calculated. In all subsequent exercise tests haemodynamic measurements were made at rest, after two minutes of exercise, at submaximal exercise, and at maximal exercise. A final set of measurements was made during recovery, one minute after maximal exercise. Blood samples for gas analysis were drawn within a minute of the submaximal haemodynamic measurements, shortly before maximal exercise. Note that in individual patients the same level of submaximal exercise was used in each test to provide a directly comparable set of data.

STATISTICAL ANALYSIS

The purpose of the statistical analysis was to detect a variation in the response to exercise over the 30 days

Table 2 Haemodynamic responses to milrinone during exercise in 12 patients with congestive heart failure. Values are mean (SEM)

Day of study	At rest	Level of exercise				Three way analysis of variance
		2 min	Submaximal	Maximal	Recovery*	
Heart rate (beats/min)						
1 (n=12)	95 (5)	119 (2)	133 (5)	146 (5)	124 (4)	NS
3 (n=12)	96 (4)	116 (3)	129 (5)	149 (5)	128 (4)	
28 (n=11)	93 (5)	118 (3)	128 (3)	150 (3)	125 (5)	
30 (n=10)	98 (4)	115 (3)	128 (4)	151 (4)	132 (5)	
2 way analysis of variance	NS	NS	NS	NS	NS	
Systolic blood pressure (mm Hg)						
1 (n=12)	139 (9)	164 (11)	170 (12)	176 (13)	150 (11)	NS
3 (n=12)	135 (10)	167 (14)	177 (15)	171 (13)	165 (13)	
28 (n=11)	130 (7)	155 (9)	169 (14)	163 (11)	156 (10)	
30 (n=10)	131 (9)	151 (10)	158 (11)	166 (14)	158 (8)	
2 way analysis of variance	NS	NS	NS	NS	NS	
Diastolic blood pressure (mm Hg)						
1 (n=12)	76 (3)	76 (4)	78 (4)	81 (4)	74 (4)	NS
3 (n=12)	76 (4)	73 (2)	72 (2)	70 (2)	77 (2)	
28 (n=11)	75 (3)	70 (3)	74 (3)	72 (3)	77 (2)	
30 (n=10)	77 (3)	70 (3)	71 (3)	75 (3)	84 (4)	
2 way analysis of variance	NS	NS	NS	NS	NS	
Cardiac index (l/min per m ²)						
1 (n=12)	1.9 (0.1)	3.6 (0.4)	4.2 (0.3)	4.8 (0.3)	3.1 (0.2)	p<0.001
3 (n=12)	2.3 (0.2)	4.4 (0.4)**	5.0 (0.4)**	5.9 (0.4)**	3.7 (0.2)	
28 (n=11)	2.0 (0.1)	3.9 (0.3)	5.0 (0.3)*	5.8 (0.4)**	3.4 (0.2)	
30 (n=10)	1.9 (0.1)	3.6 (0.4)	4.1 (0.4)	4.9 (0.3)	3.1 (0.3)	
2 way analysis of variance	p<0.05	p<0.001	p<0.001	p<0.001	p<0.05	
Stroke volume index (ml/beat per m ²)						
1 (n=12)	21 (2)	30 (3)	32 (2)	33 (2)	25 (2)	p<0.001
3 (n=12)	25 (2)	38 (3)**	39 (3)*	39 (2)*	29 (2)	
28 (n=11)	21 (2)	33 (3)	39 (3)*	39 (2)	27 (2)	
30 (n=10)	20 (1)	31 (3)	33 (3)	33 (2)	25 (1)	
2 way analysis of variance	NS	p<0.01	p<0.05	p<0.01	NS	
Pulmonary capillary wedge pressure (mm Hg)						
1 (n=12)	4 (2)	11 (3)	15 (3)	20 (3)	7 (2)	p<0.001
3 (n=12)	3 (1)	12 (3)	16 (3)	19 (3)	8 (2)	
28 (n=11)	3 (2)	12 (2)	15 (3)	20 (2)	7 (3)	
30 (n=10)	6 (2)	16 (2)	18 (2)	25 (2)	13 (3)*	
2 way analysis of variance	NS	NS	NS	p<0.01	p<0.01	
Systemic vascular resistance (units)						
1 (n=12)	26 (2)	17 (3)	14 (2)	13 (1)	17 (2)	p<0.001
3 (n=12)	22 (2)	13 (1)*	11 (1)***	10 (1)***	15 (1)	
28 (n=11)	24 (1)	14 (2)	11 (1)***	9 (1)***	16 (1)	
30 (n=10)	26 (2)	15 (2)	12 (1)	12 (1)	17 (2)	
2 way analysis of variance	NS	p<0.01	p<0.001	p<0.001	NS	

*One minute after peak exercise.

Statistical differences by 3 way and 2 way analyses of variance—significance of individual changes with respect to day 1: *p<0.05, **p<0.01, ***p<0.001.

of the study. A three way analysis of variance was used to detect any variation in the haemodynamic measurements between the study days corrected for time. When a significant difference ($p<0.05$) between days was found a two way analysis of variance was used to investigate the variation at each time point during the exercise period. Finally, a modified *t* test, by the Bonferroni method, was used to detect the source of the differences at those times, where significant variation was present.¹⁵

Results are expressed as mean (SEM).

Results

HAEMODYNAMIC RESPONSES

Table 2 summarises the haemodynamic responses to treadmill exercise during the course of the study. The

Figure shows the effects of milrinone on stroke volume index and pulmonary capillary wedge pressure during exercise.

Control (day 1)—Despite the pronounced depression of resting cardiac index and stroke volume index before milrinone treatment, the pulmonary capillary wedge pressure (measured in the upright position) was normal owing to the influence of diuretic treatment. During exercise, however, the pulmonary capillary wedge pressure increased rapidly to 20(3) mm Hg at peak exercise, though peak responses for cardiac index (4.8(0.3) l/min per m²) and stroke volume index (33(2) ml/beat per m²) were severely attenuated. Systemic oxygen consumption at submaximal exercise was only 56.7(5.4) ml/min per kg (Table 3). In all cases it was the early onset of fatigue and dyspnoea that limited exercise tolerance (6.9(0.8)

Table 3 Changes in systemic oxygen utilisation at submaximal and maximal exercise capacity. Values are mean (SEM)

	Day 1	Day 3	Day 28	Day 30	Two way analysis of variance
Arteriovenous oxygen difference (vol/100 ml)	13.1 (0.7)	13.4 (0.6)	13.6 (0.7)	13.8 (0.7)	NS
Systemic oxygen consumption index (ml/min per kg)	56.7 (5.4)	67.8 (6.3)	68.2 (5.8)	58.5 (6.3)	p<0.05
Maximal exercise capacity (min)	6.9 (0.8)	8.4 (0.9)	8.9 (0.9)	8.4 (1.0)	p<0.001

minutes; Table 3). Heart rate and blood pressure rose normally with exercise and systemic vascular resistance declined.

After milrinone (days 3 and 28)—Milrinone produced a small increase in resting cardiac index compared with control values but did not significantly influence the resting data in other respects. Exercise responses, however, showed important differences. Thus by day 3 of the study both cardiac index and stroke volume index were significantly higher than control values at every level of exercise. This improvement in the output response to exercise was sustained, and the measurements on day 28 were similar (Fig.). A sustained reduction in exercise systemic vascular resistance also occurred during milrinone treatment, though the changes in this variable were small. The arteriovenous oxygen difference at sub-

maximal exercise was not influenced by milrinone, but systemic oxygen consumption increased significantly (Table 3). Exercise responses in other respects were unaffected.

After milrinone (day 30)—Two days after milrinone withdrawal all variables with the exception of pulmonary capillary wedge pressure reverted towards pretreatment values and were not significantly different from these values at rest or during exercise. The pulmonary capillary wedge pressure, however, was always appreciably higher than pretreatment values, and the difference was significant for the measurements at peak exercise and one minute after peak exercise (Table 2).

DRUG RELATED SIDE EFFECTS

No drug related side effects occurred during the four week treatment period. In particular, the patients experienced no gastrointestinal symptoms, and there was no thrombocytopenia ($<100 \times 10^9/l$). Mean plasma platelet concentrations ($\times 10^9/l$) in 10 patients were 270(17) before milrinone treatment and 217(17) after 28 days. This change was not statistically significant.

Discussion

This study has shown that milrinone treatment in heart failure is well tolerated and improves the haemodynamic response to treadmill exercise. Maximal exercise capacity is prolonged. Importantly, these beneficial effects are sustained during long term treatment. The data suggest that a drug induced increase in the perfusion of working skeletal muscle is largely responsible for the improvement in exercise tolerance.

The patients included in the present study had moderate to severe left ventricular dysfunction and were limited principally by exertional fatigue and dyspnoea. The main aim of this investigation was, therefore, to determine the effects of milrinone treatment on the haemodynamic responses to exercise. Information of this type is not currently available. Though milrinone increased cardiac index at rest, the changes in other resting measurements were not significant in contrast to the effects of acute milrinone challenge.¹⁴ The reason for this difference is not clear but might relate either to upright posture and height

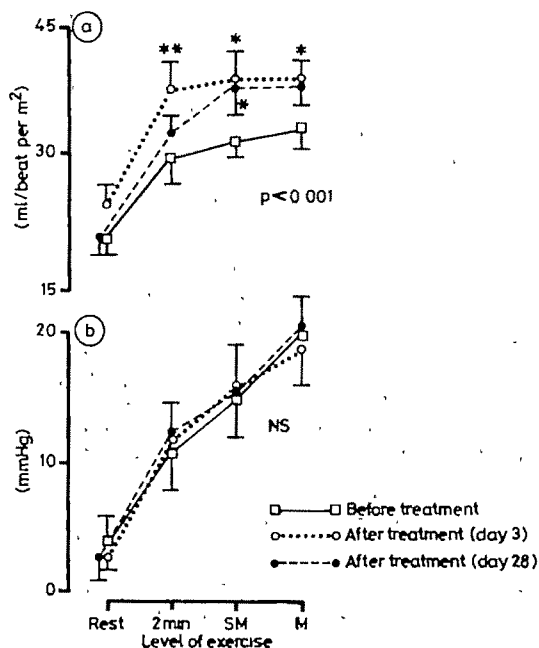


Figure Effects of milrinone on (a) stroke volume index and (b) mean pulmonary capillary wedge pressure at rest, after two minutes (2 min) of exercise, at submaximal (SM) exercise, and at maximal (M) exercise. Significance of difference between values after treatment and pretreatment values: *p<0.05, **p<0.01. Values are mean (SEM).

tened vascular tone or to the four to five hour delay between drug dosage and haemodynamic measurements in the exercise study. During exercise milrinone produced significant increments in cardiac index without affecting left ventricular filling pressure (as measured by pulmonary capillary wedge pressure). This must reflect an improvement in left ventricular performance. The heart rate response to exercise was not influenced by the drug indicating that the improvement in cardiac index was due entirely to an increase in stroke volume index. Precise analysis of the mechanisms of these beneficial haemodynamic effects is, however, not possible, but by inference from the acute responses at rest in the same group of patients it is likely that a combination of positive inotropism and vasodilatation was responsible for the changes observed.¹⁴

The improvement in left ventricular performance during milrinone treatment was associated with an increase in systemic oxygen consumption at submaximal exercise. Previous investigators have also reported increments in exercise oxygen consumption in response to milrinone.¹¹ Systemic oxygen consumption is determined by cardiac output and oxygen extraction. Since the oxygen extraction of metabolising tissues is not impaired in patients with heart disease changes in systemic oxygen consumption usually reflect changes in cardiac output or, more precisely, changes in perfusion of the metabolising tissues.¹⁶ During exercise the increased oxygen demand derives primarily from the extra requirements of working skeletal muscle. Thus our finding of a milrinone induced rise in systemic oxygen consumption suggests that the drug did not significantly alter the physiological distribution of arterial blood flow during exercise and that the increase in cardiac output was delivered where it was needed—to working skeletal muscle. This contrasts with the effects of vasodilators that do not always increase oxygen consumption or maximal exercise capacity in patients with heart failure.^{17,18} In a recent study with felodipine (a vasodilating calcium antagonist) using a similar protocol we found a reduction in systemic arteriovenous oxygen difference at submaximal exercise such that oxygen consumption was unaffected despite increments in cardiac output.¹⁹ It was argued from these data that felodipine, like hydralazine and prazosin,¹⁸ might redistribute flow away from skeletal muscle during exercise. Milrinone does not share this potentially adverse effect and may, therefore, be of greater therapeutic value than vasodilators since systemic oxygen consumption is a major predictor of functional capacity in patients with heart failure.²⁰

The beneficial effects of milrinone on exercise cardiac index and oxygen consumption must have accounted in part for the improvement in exercise

capacity measured in the present study. Previous investigators have reported a similar symptomatic improvement during milrinone treatment in heart failure.^{10,12} Drug withdrawal, however, did not cause a significant deterioration in exercise capacity despite return of cardiac index and oxygen consumption towards control values. Thus other factors, apart from the direct effects of milrinone, must have influenced the changes in maximal exercise capacity observed in the present study. The importance of training and patient motivation, for example, is impossible to quantify, and this inevitably limits the sensitivity of serial exercise testing as a measure of drug induced changes in left ventricular function.²¹ More useful information is provided by direct haemodynamic measurements and gas analysis. Only in a randomised controlled study, however, can the independent effect of milrinone on exercise capacity be properly evaluated.

The natural history of congestive heart failure involves a variably progressive deterioration in left ventricular function that is often difficult to distinguish from drug tolerance in studies of this type. For this reason a four week treatment period was chosen since baseline cardiac status would not be expected to change appreciably during this relatively short period. Our data show that the improvement in exercise haemodynamics produced by milrinone was sustained during four weeks' treatment without evidence of tachyphylaxis. This finding, which accords with that of other investigators,¹⁰⁻¹² is clearly of clinical importance for the long term management of heart failure and may distinguish milrinone from some other drugs commonly used in this condition.²⁻⁴

Two days after milrinone had been withdrawn exercise haemodynamic variables returned towards control values confirming that the changes observed during treatment were a direct result of the drug intervention. Pulmonary capillary wedge pressure, however, which had not changed during treatment, was higher than control values after drug withdrawal even though diuretic dosage was constant throughout the study. The difference was significant only at peak exercise and one minute after peak exercise and may simply reflect the extra stress, compared with that before treatment, caused by the patients' endeavours to equal the peak exercise time achieved during milrinone treatment. (The potential influence of patient motivation on exercise tolerance has already been discussed.) Alternatively, the finding could indicate a deterioration in left ventricular function to a level worse than that before treatment. Deterioration of this type has been reported after amrinone withdrawal in long term studies²² (though this could not be confirmed in a larger placebo controlled study), and, more recently, Sinoway *et al* observed a similar

response to milrinone withdrawal.¹⁰ These authors attributed the phenomenon to progression of underlying disease even though the average treatment period was only seven weeks. Our patients were treated for only four weeks—a period that resulted in no measurable deterioration in baseline left ventricular function in a similar group of patients treated with felodipine.¹⁹ The possibility remains, therefore, that milrinone itself is responsible for this adverse effect. Increments in myocardial oxygen demand seen on acute milrinone challenge¹⁴ would be a potential mechanism for an accelerated decline in baseline functional status as has been suggested on theoretical grounds with other inotropic agents.²³ More work is required to resolve this issue.

An important finding in the present study was the absence of drug related side effects. Though the haemodynamic effects of milrinone are in most respects similar to those of its parent compound amrinone the toxic properties of amrinone, particularly thrombocytopenia and gastrointestinal disturbance, have limited its clinical application.⁸ Our patients tolerated milrinone without complaint and plasma platelet concentrations were well maintained. Thus the beneficial haemodynamic effects of milrinone are combined with a high level of patient acceptability. These properties suggest a potentially useful role for milrinone treatment in the long term management of congestive heart failure. Confirmation of this role, however, must await the results of randomised controlled studies.

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Nuclear magnetic resonance in hypertrophic cardiomyopathy

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SUMMARY The large differences in the spin lattice relaxation times (T_1) of blood and myocardium (measured by nuclear magnetic resonance) allow the heart to be visualised without the use of contrast media. The findings using nuclear magnetic resonance in 11 unselected patients with hypertrophic cardiomyopathy were compared with those in equal numbers of normal subjects and patients with electrocardiographic features of left ventricular hypertrophy. In patients with hypertrophic cardiomyopathy characteristic septal hypertrophy was noted together with variable and sometimes pronounced hypertrophy of the left ventricular free wall, which is consistent with the heterogeneous nature of this disease. The mean (SD) ratio of septal to free wall thickness was 1.5(0.8) for patients with hypertrophic cardiomyopathy, 0.8(0.2) for those with left ventricular hypertrophy, and 0.9(0.2) for normal subjects. Although septal measurements by nuclear magnetic resonance were greater than those obtained by echocardiography there was a significant correlation between the two. Septal and free wall area were significantly smaller in normal subjects. There were no differences in septal or free wall T_1 values between the three groups.

Non-gated nuclear magnetic resonance can detect septal and free wall hypertrophy. With the addition of multiple slice acquisition, rapid estimation of myocardial mass will be possible allowing the potentially important assessment of progression or regression of myocardial hypertrophy.

Hypertrophic cardiomyopathy is characterised by hypertrophy of myocardium, particularly of the inter-ventricular septum, without apparent cause. Distinct histological appearances—such as cardiac muscle cell disorganisation, again mainly of the septum—have been reported.¹ The diagnosis may be confirmed by echocardiography if the typical features (systolic anterior motion of the mitral valve, early aortic valve closure, and disproportionate thickening of the septum relative to the left ventricular free wall) are present. When few of the features are present or if echocardiography is technically difficult than doubt remains. In 1982 Goodwin suggested that angiocardiology was still the most useful investigation.²

Nuclear magnetic resonance can be used for both non-invasive visualisation of cardiac structures and tissue characterisation; the second can be achieved by using the spin lattice relaxation time (T_1). The large

differences in the T_1 values of myocardium and blood allow clear separation between cardiac muscle and cavity without the use of contrast medium.³

Using nuclear magnetic resonance we therefore examined the appearances of hypertrophic cardiomyopathy by measuring septal and free wall thickness and contrasting T_1 values with those found in concentric left ventricular hypertrophy and normal hearts.

Patients and methods

SUBJECTS

Three groups were examined. The first consisted of 11 unselected patients attending a cardiac review clinic with an established diagnosis of hypertrophic cardiomyopathy based on clinical, echocardiographic, and in two cases angiographic findings (Table 1). The second group consisted of 11 patients with left ventricular hypertrophy based on the electrocardiographic criteria of Romhilt and Estes,⁴ of whom nine had World Health Organisation stage III hypertension, one aortic stenosis, and one aortic coarctation. The third group consisted of 11 age matched healthy

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Table 1 Echocardiographic and nuclear magnetic resonance measurements in 11 patients with hypertrophic cardiomyopathy

Case No	Age (yr)	M Mode echocardiography				Nuclear magnetic resonance			
		Septal thickness (mm)	Posterior LV wall thickness (mm)	SAM	Early closure of aortic valve	Septum		LV free wall	
						Thickness (mm)	Area (cm ²)	Thickness (mm)	Area (cm ²)
1*	50	14	16	NO	NO	14	4.38	23	4.07
2	55	24	15	NO	YES	23	4.96	7	4.40
3	26	32	20	NO	YES	32	7.35	20	7.17
4	52	30	12	YES	YES	41	7.69	54	8.82
5	45	18	20	NO	NO	26	5.14	23	7.17
6	19	30	16	NO	NO	30	4.62	14	5.57
7*	48	20	18	NO	NO	26	4.93	15	4.53
8	32	32	14	YES	YES	46	9.03	41	8.39
9	68	15	12	YES	YES	29	5.36	27	6.00
10	19	26	12	YES	YES	37	8.21	20	5.67
11	45	14	12	YES	YES	38	6.55	18	5.18

*Sisters

LV, left ventricular, SAM, systolic anterior motion

volunteers drawn mainly from hospital staff. In all cases consent was obtained and the study approved by our institute's ethical committee.

NUCLEAR MAGNETIC RESONANCE

Nuclear magnetic resonance was carried out using a commercial (M&D Technology) low field (0.08T) resistive imaging system. Cardiac gating was not used. Three transverse sections with a slice of 16 mm were obtained from each subject with a separation of 20 mm between each section. The pulse sequence used was an interlaced saturation recovery and inversion recovery sequence each with a repetition rate of 1 s and a tau value of 200 ms for the latter. For each section four images were obtained at the end of the 4 min 16 s acquisition: proton density, calculated T_1 , inversion recovery, and a "difference" image (proton density-inversion recovery). The inversion recovery and difference images contain both T_1 and proton density information. Of the four images, the calculated T_1 image gave the best contrast between blood and myocardium. The long term precision of T_1 estimation using this particular technique has been found to be 2.7% for a T_1 value of 300 ms.

The section giving best definition between septum and left ventricular cavity was selected for each patient and studied in more detail. Initially, an estimate of the mean and range of T_1 values for myocardium and ventricular blood was obtained in the 33 subjects. The mean (SD) T_1 value for myocardium was 345(28) and for blood 635(124). The window on the T_1 images was set so that all pixels with a T_1 value >450 ms appeared uniformly bright enabling myocardium and blood to be clearly separated. Irregular regions of interest were drawn around the interventricular septum and free wall of the left ventricle using the computer. Computer derived measurements of septal and free wall thickness and area

were made together with total cardiac diameter.

ECHOCARDIOGRAPHY

M mode and real time echocardiography were carried out in the left-oblique position within two weeks of the nuclear magnetic study. Septal and free wall diameters were measured from M mode recordings using an Irex-3 phased array system with a 2.5 MHz transducer in the groups with hypertrophic cardiomyopathy and left ventricular hypertrophy. Recordings were made at end diastole at a level just above the mitral valve. Septal and free wall thickness were measured in three consecutive cycles and the mean values noted for each subject. Five of the patients with hypertrophic cardiomyopathy showed systolic anterior motion of the anterior mitral leaflet and seven some degree of early closure of the aortic valve. None of these abnormalities was seen in patients with left ventricular hypertrophy. Two patients did not have echocardiographic features typical of hypertrophic cardiomyopathy, the diagnosis having been established at angiography (cases 1 and 5).

STATISTICAL ANALYSIS

A non-paired Wilcoxon rank test was used for comparison between groups. Student's *t* test was used for comparison of T_1 values between septum and left ventricular free wall with all groups combined.

Results

In eight patients with hypertrophic cardiomyopathy nuclear magnetic resonance showed characteristic appearances with pronounced septal hypertrophy and a variable degree of left ventricular free wall hypertrophy (Figs. 1 and 2). Table 1 shows the results and patient details for the group with hypertrophic car-

Table 2 Septal and left ventricular free wall spin lattice relaxation times (T_1) in three groups of patients. Values are mean (SD)

	Septal T_1 (s)	Free wall T_1 (s)
Normal subjects	374 (18)	331 (29)
Patients with ventricular hypertrophy	355 (31)	333 (22)
Patients with hypertrophic cardiomyopathy	352 (27)	342 (24)

diomyopathy. In those patients with secondary left ventricular hypertrophy the free wall and septum appeared of equal thickness, but the muscle mass was greater than in normal subjects. The differences in area and dimension between patients with hypertrophic cardiomyopathy, left ventricular hypertrophy, and normal hearts (Figs. 3 and 4) are summarised below.

SEPTAL AND FREE WALL THICKNESS

There was considerable variation in the thickness of both septum and left ventricular free wall measured by nuclear magnetic resonance in the group with hypertrophic cardiomyopathy (Table 1). Although septal measurements were greater than those obtained with echocardiography there was a significant correlation between the two ($r=0.71$, $p<0.001$). The mean ratio of septal to free wall thickness measured by nuclear magnetic resonance and M mode echocardiography was similar at $1.5(0.8)$ and $1.6(0.6)$ respectively. The mean ratio of septal to free wall thickness as measured by magnetic resonance imaging was $0.8(0.2)$ for patients with left ventricular hypertrophy and $0.9(0.3)$ for normal subjects. In view of the variability of this ratio in patients with hypertrophic cardiomyopathy, there was no statistically significant difference detected between the three groups.

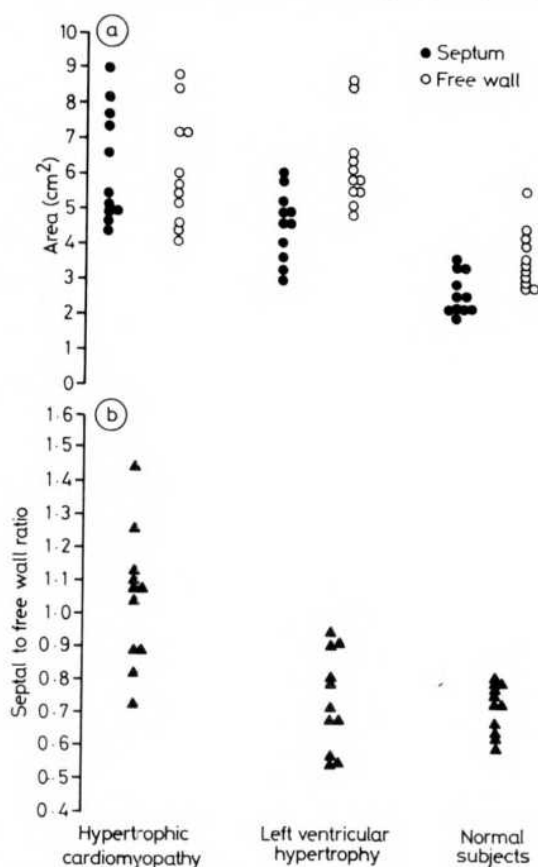


Fig. 2 (a) Septal and free wall area and (b) ratio of septal to free wall area in individual patients with hypertrophic cardiomyopathy, those with left ventricular hypertrophy, and normal subjects.

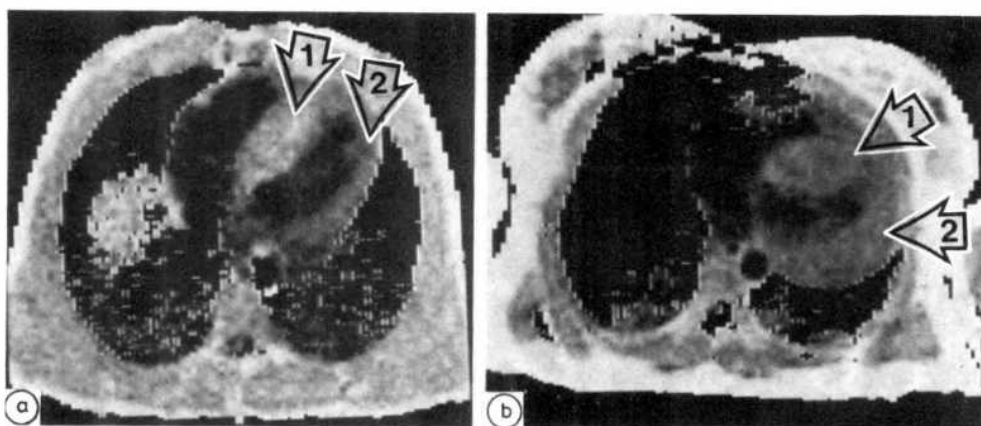


Fig. 1 Typical appearance of hypertrophic cardiomyopathy by nuclear magnetic resonance showing pronounced septal hypertrophy (arrow 1) (a) with mild left ventricular free wall hypertrophy (arrow 2) (case 10) and (b) with pronounced left ventricular free wall hypertrophy (arrow 2) (case 8).

SEPTAL AND FREE WALL AREA

There was a significant difference in septal area between normal subjects and both patient groups. Measured area in normal subjects was 2.7 cm^2 compared with 4.6 cm^2 ($p < 0.05$) and 6.1 cm^2 ($p < 0.05$) for patients with left ventricular hypertrophy and hypertrophic cardiomyopathy respectively. Corresponding values for left ventricular free wall area were 3.7 cm^2 , 6.3 cm^2 ($p < 0.05$), and 6.1 cm^2 ($p < 0.05$).

TOTAL CARDIAC DIAMETER

The diameter as measured from the right ventricular border to the mid portion of the left ventricular free wall was greater in both patient groups at $138(10) \text{ mm}$ and $130(14) \text{ mm}$ for patients with hypertrophic cardiomyopathy and left ventricular hypertrophy respectively compared with $120(12) \text{ mm}$ for normal subjects. The difference did not reach statistical significance.

SPIN LATTICE RELAXATION TIME (T_1)

Table 2 shows the mean values for T_1 . There was no significant difference between patient groups, although septal T_1 was consistently higher than free wall T_1 for all groups ($p < 0.01$).

Discussion

This study shows the ability of nuclear magnetic resonance to outline the interventricular septum and left ventricular free wall and to detect differences in myocardial thickness in patients with increased afterload and hypertrophic cardiomyopathy when contrasted with normal subjects. The pronounced contrast between flowing blood, which gives a high signal intensity, and the chamber walls allows hypertrophy to be demonstrated since there is also contrast between myocardium and surrounding tissues.

Within the group of patients with hypertrophic cardiomyopathy large variations in septal area were found. In those cases in which a diagnosis of hypertrophic cardiomyopathy could confidently be made by nuclear magnetic resonance the findings on echocardiography were more impressive (Table 1). Our unselected population of patients with hypertrophic cardiomyopathy represented the full spectrum of the disease, which is known to be heterogeneous.⁵ This variability in septal and free wall size was detected both by echocardiography and by nuclear magnetic resonance.

Steiner, in outlining the applications and potential of nuclear magnetic resonance in cardiac imaging, described the concentric nature of left ventricular hypertrophy in patients with hypertension and aortic stenosis and the non-uniform septal and free wall hypertrophy of hypertrophic cardiomyopathy.⁶

Although these patterns may occur in typical examples, it is important to recognise that both the extent and position of myocardial hypertrophy are variable as illustrated by nuclear magnetic resonance (Figs. 1 and 2).

Stone *et al* recently reported the appearances of hypertrophic cardiomyopathy obtained with non-gated computed tomography using contrast medium in nine patients.⁷ Visualisation of the septum was good and showed the variability of the position of maximal septal hypertrophy. Definition of the left ventricular free wall was, however, poor and inadequate for measurements. By using the differences in the relaxation index T_1 between flowing blood and ventricular muscle, nuclear magnetic resonance can allow clear visualisation of both septum and free wall without the use of contrast agents.

It was not the purpose of this study to compare nuclear magnetic resonance with echocardiography as there is a large difference in their cost and stage of development. There is also a wide variation in purchase and installation costs between different nuclear magnetic resonance systems and the variables they measure. The system we used is a low cost low magnetic field system. Echocardiography has contributed to the understanding of hypertrophic cardiomyopathy (for example, in determining the cause and level of obstruction when present⁸) and is of value in making the diagnosis. Echocardiographic features are not, however, specific individually.⁵ M mode echocardiography gives diagnostic information in over 85% of patients, but precise measurements of left ventricular dimensions are possible in only 60–65% of patients.⁹ Real time echocardiography improves diagnostic ability, and because of its rapidity and widespread availability echocardiography will remain the commonest and most practical technique for confirming hypertrophic cardiomyopathy. Nevertheless, nuclear magnetic resonance is possible in most patients and may be helpful in those in whom echocardiographic quality is poor.

The differences observed between our three groups were from images taken without cardiac gating. The extent by which gating improves resolution in nuclear magnetic resonance is not yet established. Some reports have emphasised the need for cardiac gating to obtain satisfactory anatomical information.¹⁰ Choyke *et al*, however, have shown that images of diagnostic quality were obtained without gating using single spin echo sequences with a very short echo time (10–20 ms).¹¹ In practice it gives a very similar echo time to that used in our own system. They had noted pronounced degradation of the image with longer echo times and concluded that the previous unfavourable reports using non-gated techniques may have been due to longer echo times used in other centres.

The ability to obtain measurements of myocardial area and thus by multiple slice acquisition to estimate myocardial mass may prove valuable in the follow up of patients with myocardial hypertrophy. Drug treatment in both patients with hypertension and those with hypertrophic cardiomyopathy should ideally result in a reduction in muscle mass. The non-invasive nature of nuclear magnetic resonance makes this an attractive method for long term assessment of such patients.

This work was funded in part by the Medical Research Council, Department of Health and Social Security, the Scottish Home and Health Department, University of Edinburgh, Melville, and the Wellcome Trusts. MB was in receipt of a Squibb Cardiovascular Fellowship.

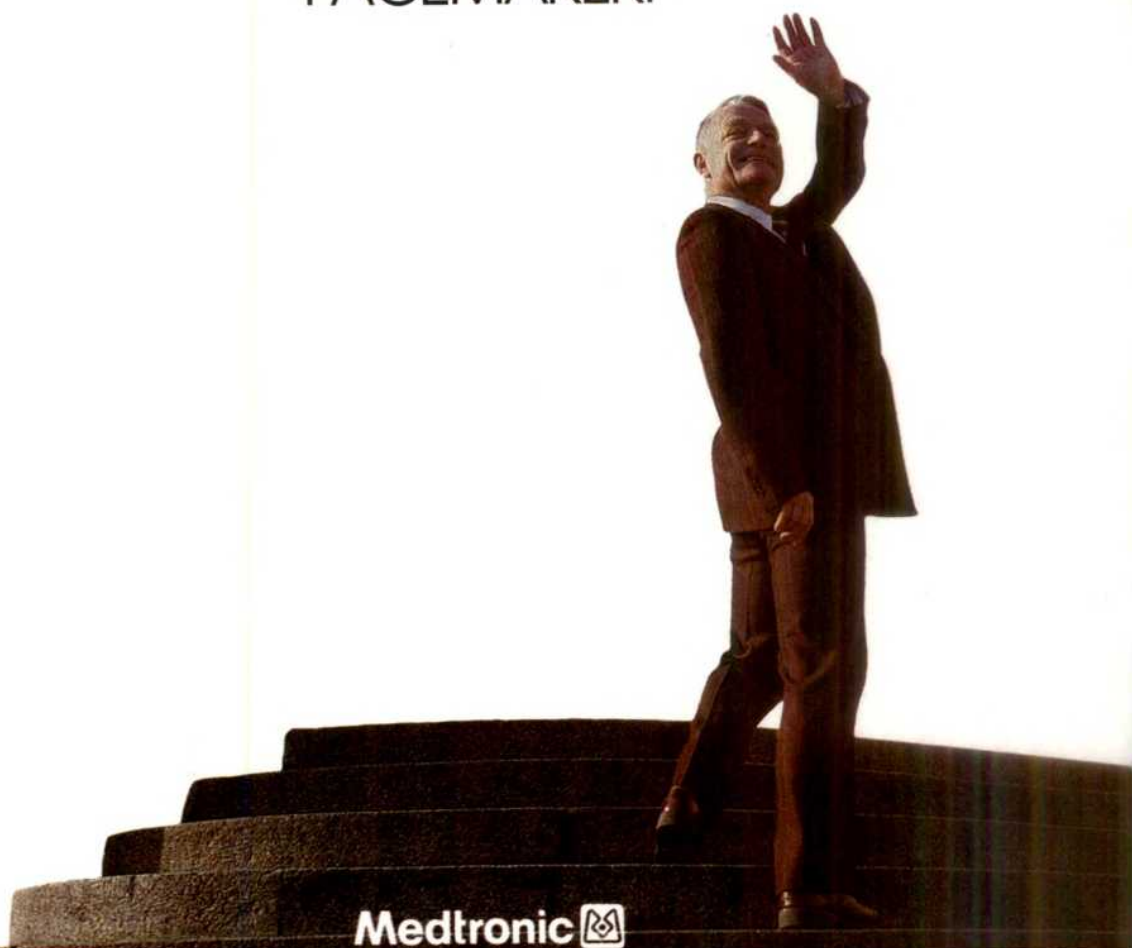
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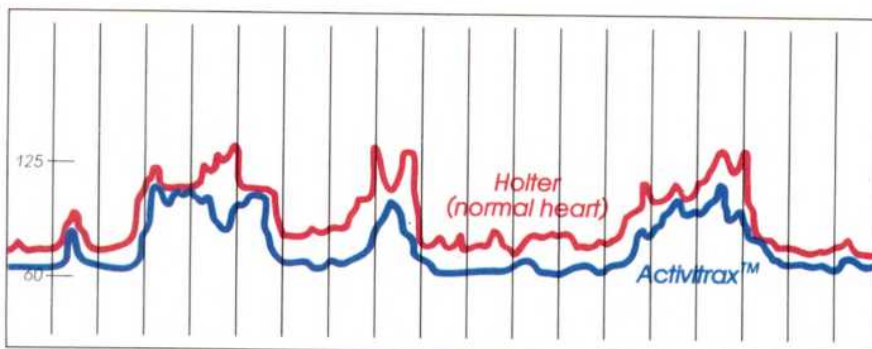
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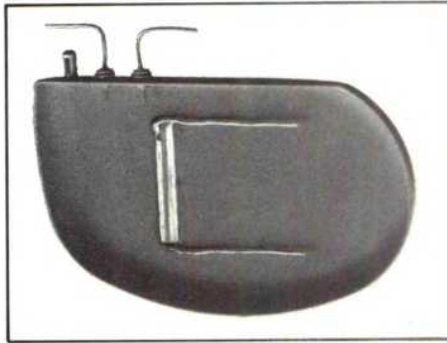
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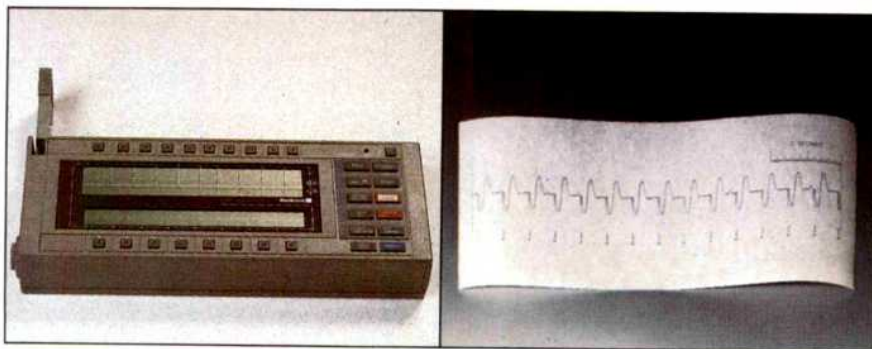
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Localisation of ventricular septal defects by simultaneous display of superimposed colour Doppler and cross sectional echocardiographic images

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SUMMARY Precise non-invasive localisation of the site of a small ventricular septal defect was attempted using a new technique that simultaneously combines conventional cross sectional echocardiography with a Doppler system by superimposing the colour coded direction and velocity of blood flow directly on to real time ultrasound images. Twenty three patients with unoperated ventricular septal defects and a further eight after surgical closure were studied; 12 children with normal hearts served as controls. A colour coded blood flow jet entering the right ventricle during systole was identified in all 23 unoperated patients, in 11 of whom the defect was too small to be visualised by conventional cross sectional echocardiography. The colour Doppler technique precisely located 19 perimembranous and five trabecular defects (one patient had two defects). Five of the postoperative patients were without clinical evidence of a significant shunt but had pansystolic murmurs. In each of these five, trans-septal shunt blood flow was demonstrated by colour Doppler images whereas in only three of these patients was the residual defect large enough to be visualised by conventional cross sectional echocardiography. Three postoperative patients had no murmurs and showed no residual shunt on colour Doppler images. This was confirmed at cardiac catheterisation. There were no false positive results among the controls.

This technique is useful for the more accurate diagnosis and location of ventricular septal defects and may help in assessing their natural or surgical closure.

Despite recent advances in ultrasound instrumentation and image quality, difficulties may be encountered in identifying small ventricular septal defects, particularly within the trabecular septum.¹⁻³ There remains a sizeable number of patients in whom the diagnosis of ventricular septal defect is based solely on clinical findings such as the character and location of the systolic murmur. Consequently, this study aimed to determine if diagnosis could be improved by the detection of trans-septal blood flow in patients with small ventricular septal defects using a new colour coded Doppler system that superimposes flow information on to conventional cross sectional images

(colour Doppler). This system has already proved useful in assessing acquired valvar diseases, particularly regurgitation.^{4,5} With its unique display, we reasoned that this system should be able precisely to locate ventricular septal defects in a way hitherto impossible, and thus we considered it to be important in the present study to assess the clinical usefulness of this novel approach.

Patients and methods

STUDY GROUPS

This work formed part of a comprehensive longitudinal follow up study on a group of 182 patients with ventricular septal defects conducted from June 1980 to August 1984 at the Hospital for Sick Children, London. Thirty one patients were randomly selected to constitute the study group.

The patients were subsequently divided into three groups. Group 1 consisted of 12 patients (age range 90

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Accepted for publication 5 February 1985

days to 12.3 years; median 2.5 years) whose ventricular septal defect had previously been visualised and anatomically located by conventional cross sectional echocardiography (Advanced Technology Laboratory mechanical sector scanner, model 600). One patient in this group also had pulmonary stenosis with a valve gradient of 45 mm Hg and peak right and left ventricular systolic pressures of 70 mm Hg and 86 mm Hg respectively. Group 2 consisted of 11 patients (age range 96 days to 15.1 years; median 4.3 years) whose ventricular septal defect had been diagnosed clinically but was too small to be visualised by conventional cross sectional echocardiography. Group 3 consisted of eight postoperative patients who had undergone surgical closure of their ventricular septal defects (age range 78 days to 6.75 years; median 2.6 years; mean time elapsed since surgery 5.9 months). A separate group of 12 children (age range 60 days to 10.5 years; median 5.6 years) with normal hearts served as controls.

ECHOCARDIOGRAPHY

The combined cross sectional and colour coded Doppler echocardiographic studies were performed by the operator before any physical examination or auscultation was carried out. Doppler signals, colour coded for the direction of blood flow, were obtained using an Aloka SSD-880 ultrasound scanner. This scanner, by incorporating a recently developed autocorrelator,⁶ encodes blood flow in terms of colour and instantaneously superimposes this information in real time across either the entire screen of a standard cross sectional echocardiographic display or a selected region. Colours were assigned in accordance with the direction of blood flow; blue was arbitrarily given to blood flowing towards the transducer, while red was given to the blood flowing away from it. Colour brightness, displayed in seven gradations, was proportional to the velocity of blood flow. The emitting frequency used was 2.5 or 3.5 MHz as appropriate. Real time signals were stored using a Sony SLO-420 Betamax video tape recorder and later transferred to a Sony U-matic format. These images were replayed on a Sony VO-5800PS recorder through a colour monitor, either at normal speed or in slow motion as required. Still frames were taken either at the time of study from an integral Polaroid camera or subsequently by photographing images frozen by the stop frame facility on the U-matic recorder directly from the monitor.

As a screening procedure in all patients, the transducer was positioned to obtain good views of the ventricular septum in all planes and axes of the heart as previously described.² Particular attention was given to the four chamber, long axis, and short axis views from the apical and parasternal approaches.

Results

Studies of the 12 control children without any cardiac abnormalities allowed the normal pattern of colour coded blood flow in the heart to be identified (Fig. 1). The presence of ventricular septal defect flow detected in the right ventricle of patients was easily distinguished from the normal pattern of right ventricular flow seen in the controls.

A colour coded blood flow jet entering the right ventricle during systole was identified in all 23 patients with unoperated ventricular septal defects irrespective of whether the defect could be seen in the septum (groups 1 and 2) (Fig. 2). In group 1 patients the ventricular septal defect was defined on cross sectional echocardiography and verified by colour Doppler images to be perimembranous in nine and trabecular in three (two central, one apical). In group 2 blood flow jets entering the right ventricle were seen in a perimembranous position in nine patients and in a central trabecular position in one (Fig. 3). In another patient, previously thought clinically to have a perimembranous ventricular septal defect, the blood flow jet was clearly seen emanating from the central muscular area with the colour Doppler technique. Another patient in group 2 showed two separate jets in the perimembranous and trabecular areas of the septum at the same time, the latter being subsequently recognised anatomically by cross sectional echocardiography once its precise location had been demonstrated by the colour coded blood flow jet. Indeed similar post-colour Doppler anatomical recognition of ventricular septal defects by conventional cross sectional echocardiography occurred in three more patients in group 2. Figure 4 shows composite findings obtained from a patient in group 1 with both ventricular septal defect and pulmonary stenosis showing that the colour Doppler technique was able clearly to visualise blood flow across the defect even in the presence of a raised right ventricular peak systolic pressure (pulmonary valve gradient 45 mm Hg at cardiac catheterisation).

In all eight postoperative patients (group 3) the patch used to close the ventricular septal defect could be seen on standard cross sectional echocardiography, and residual defects were visualised in three of these. Systolic murmurs were audible in these three and in two other patients. Systolic flow jets emanating from the patch site were seen in the right ventricle of all five of these patients with systolic murmurs (Fig. 5). In the three postoperative patients without systolic murmurs no blood flow jets indicative of a ventricular septal defect were seen on colour Doppler images (Fig. 6). The absence of any residual defect in each of these three patients was also confirmed at cardiac catheterisation.

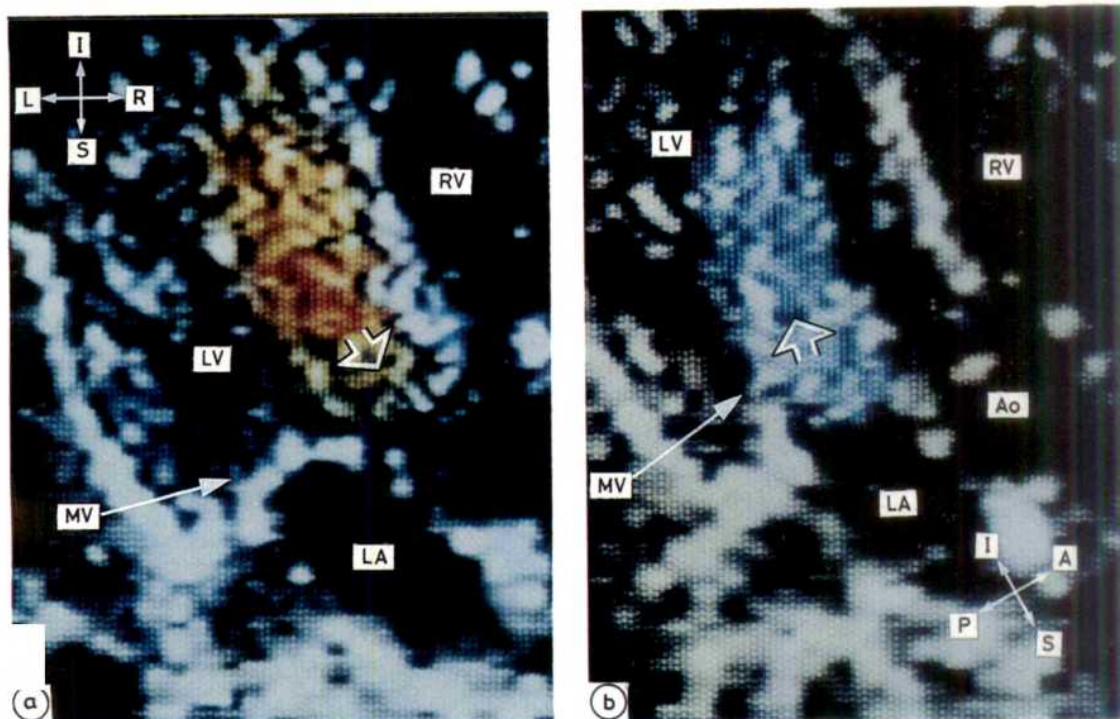


Fig. 1 Colour Doppler display of intracardiac blood flow in a normal child. Blood flow towards the transducer is depicted in blue while flow away is in yellow or red (open arrow). (a) An apical long axis cut shows normal left ventricular inflow during diastole. (b) An apical four chamber cut in the same child shows normal left ventricular outflow during systole. LA, left atrium; MV, mitral valve; LV, left ventricle; RV, right ventricle; Ao, aorta; A, anterior; P, posterior; I, inferior; S, superior; L, left; R, right.

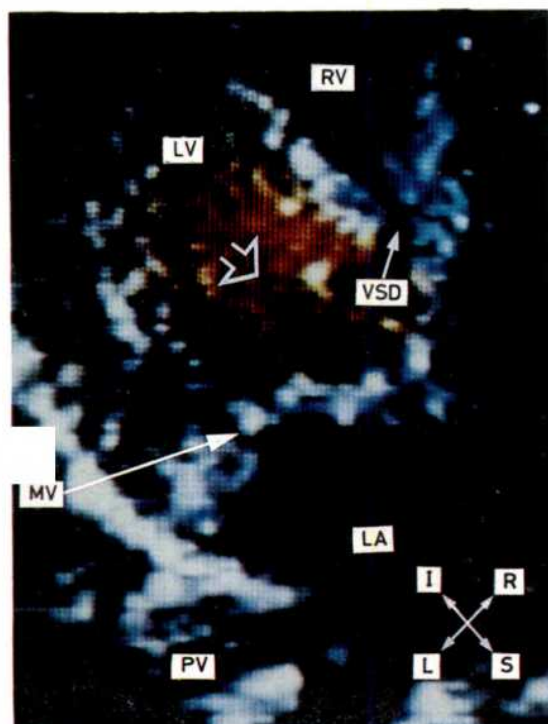


Fig. 2 Colour Doppler images of blood flow across a perimembranous ventricular septal defect in an unoperated patient. In an apical four chamber cut systolic left ventricular outflow away from the transducer is seen in red and yellow (open arrow) while a jet of shunt flow towards the transducer emanating into the right ventricle is seen in blue. LA, left atrium; PV, pulmonary vein; MV, (closed) mitral valve; LV, left ventricle; RV, right ventricle; VSD, ventricular septal defect; I, inferior; S, superior; L, left; R, right.

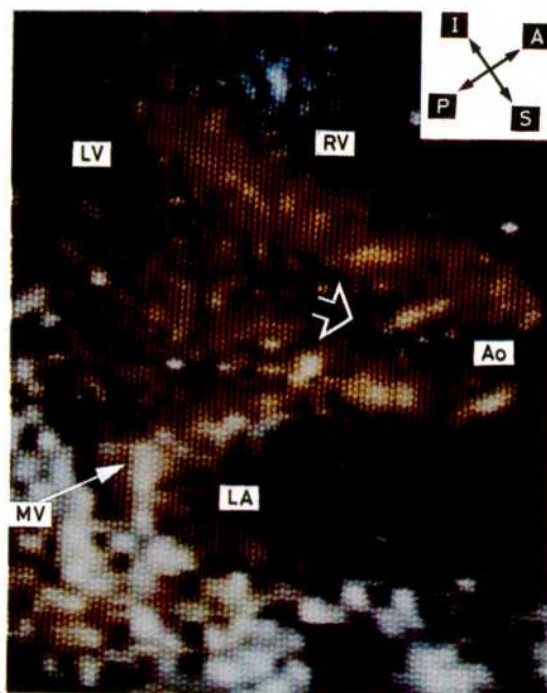
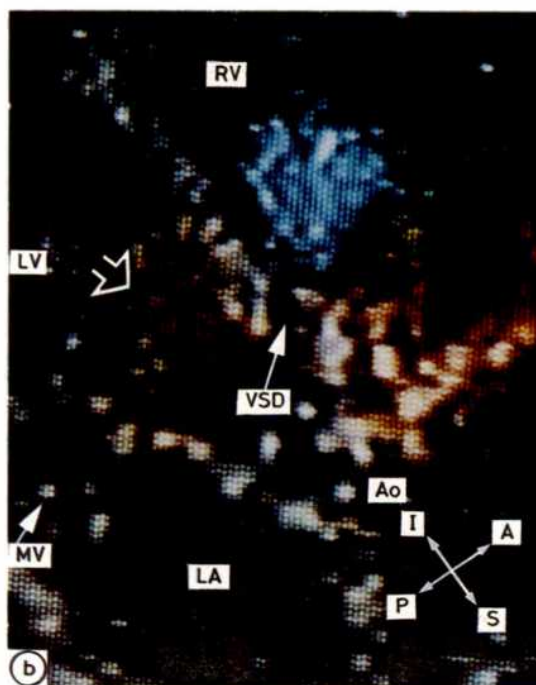
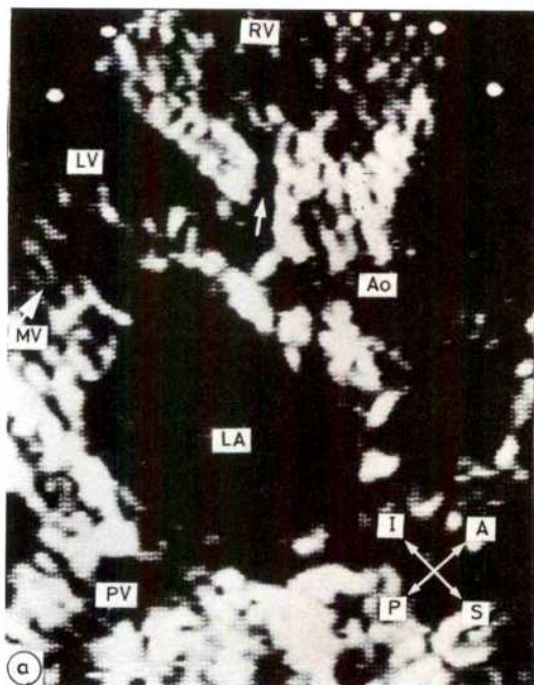


Fig. 3 Colour Doppler image of blood flow across a central trabecular ventricular septal defect in an unoperated patient. In an apical long axis cut left ventricular outflow away from the transducer is seen in red and yellow (open arrow) while a jet of shunt flow towards the transducer emanating into the right ventricle is seen in blue. LA, left atrium; MV, (closed) mitral valve; LV, left ventricle; RV, right ventricle; Ao, aorta; A, anterior; P, posterior; I, inferior; S, superior.

Fig. 4 Colour Doppler images of blood flow across a perimembranous ventricular septal defect in an unoperated child with a raised right ventricular peak systolic pressure (RV, 70 mm Hg; LV, 85 mm Hg) due to pulmonary stenosis (pulmonary valve gradient 45 mm Hg). (a) An apical long axis cut shows the location of the defect. (b) A similar cut shows blood flow in the left ventricular outflow tract in systole (open arrow) in red and yellow while, despite significant pulmonary stenosis, a jet of shunt flow towards the transducer may be clearly seen in blue emanating into the right ventricle at the site of the defect. LA, left atrium; PV, pulmonary vein; MV, mitral valve; LV, left ventricle; RV, right ventricle; Ao, aorta; VSD, ventricular septal defect; A, anterior; P, posterior; I, inferior; S, superior.



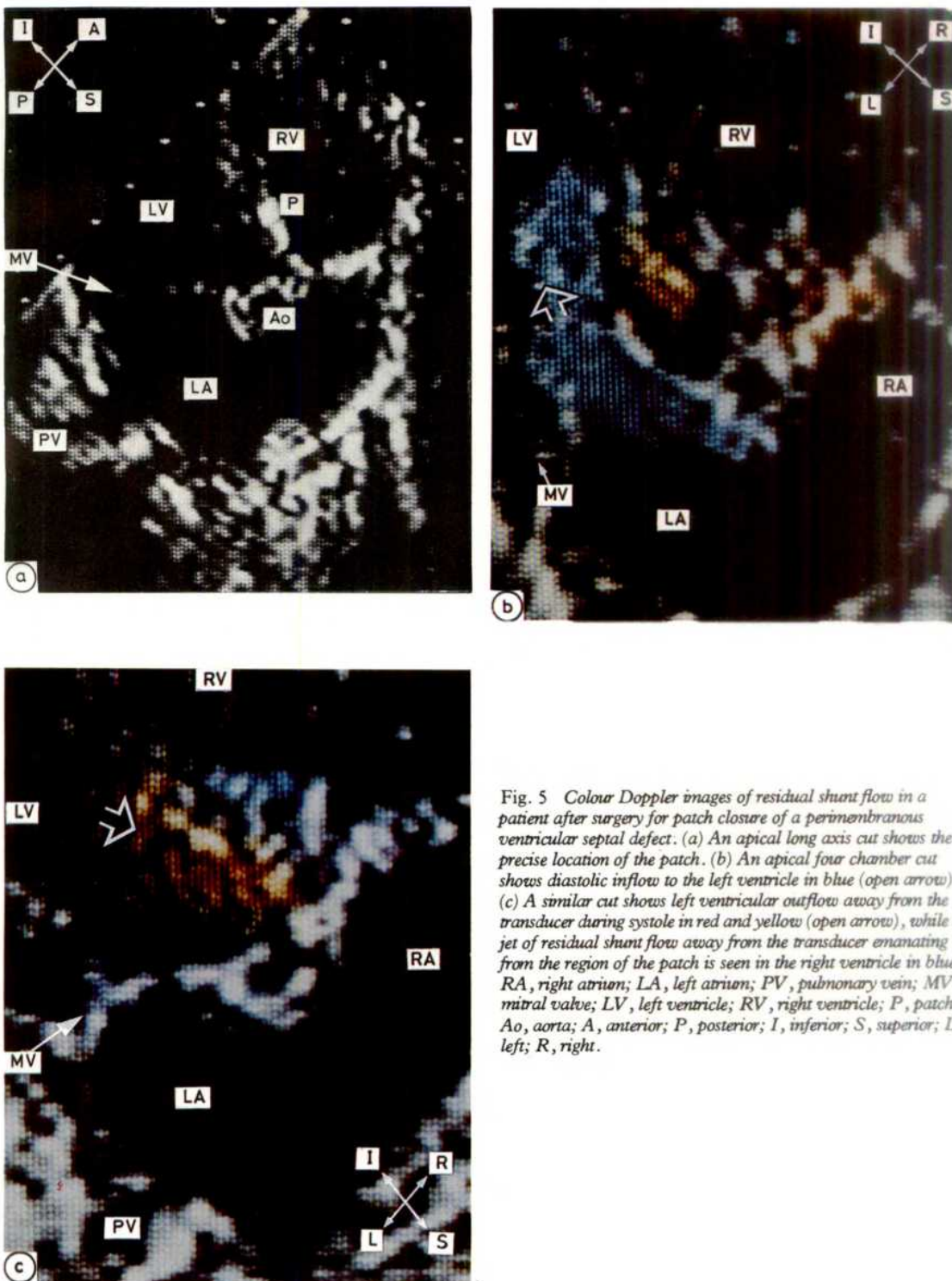


Fig. 5 Colour Doppler images of residual shunt flow in a patient after surgery for patch closure of a perimembranous ventricular septal defect. (a) An apical long axis cut shows the precise location of the patch. (b) An apical four chamber cut shows diastolic inflow to the left ventricle in blue (open arrow). (c) A similar cut shows left ventricular outflow away from the transducer during systole in red and yellow (open arrow), while a jet of residual shunt flow away from the transducer emanating from the region of the patch is seen in the right ventricle in blue. RA, right atrium; LA, left atrium; PV, pulmonary vein; MV, mitral valve; LV, left ventricle; RV, right ventricle; P, patch; Ao, aorta; A, anterior; P, posterior; I, inferior; S, superior; L, left; R, right.

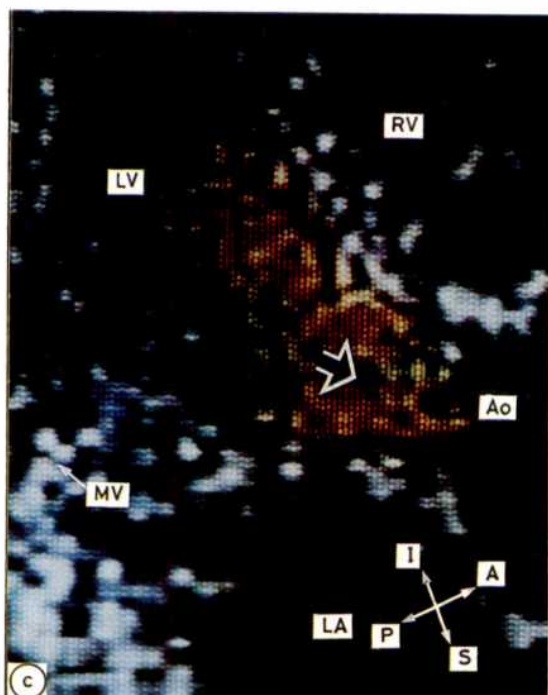
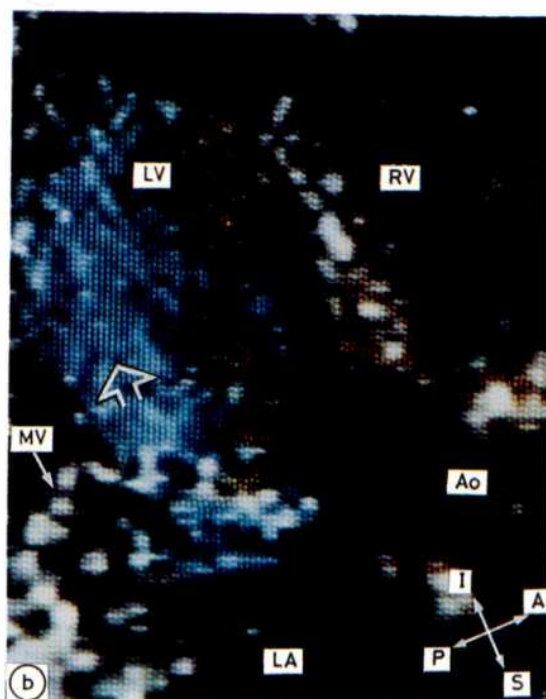
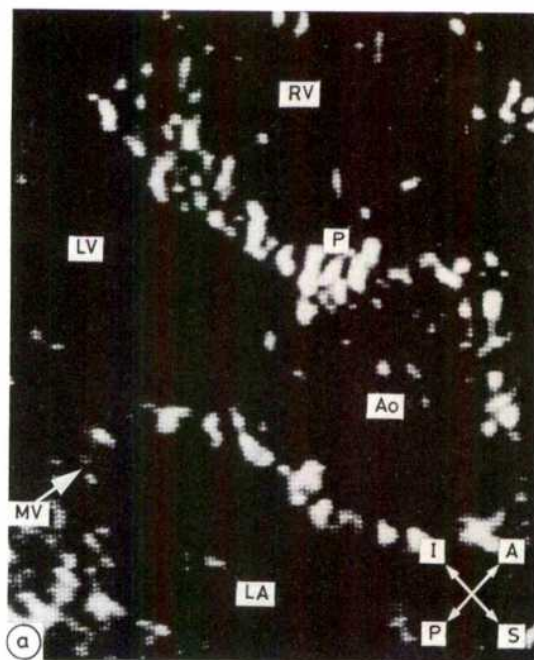


Fig. 6 Colour Doppler image in a patient after surgery for patch closure of a perimembranous ventricular septal defect indicating a patent patch by the absence of residual shunt flow into the right ventricle. (a) An apical long axis cut shows the precise location of the patch. (b) A similar cut shows diastolic inflow to the left ventricle towards the transducer in blue (open arrow). (c) A similar cut shows left ventricular outflow away from the transducer during systole in red and yellow (open arrow), but in contrast to Fig. 5c, no residual shunt could be detected in the right ventricle. The patency of the patch closure was also confirmed at cardiac catheterisation. LA, left atrium; MV, mitral valve; LV, left ventricle; RV, right ventricle; P, patch; Ao, aorta; A, anterior; P, posterior; I, inferior; S, superior.

Discussion

Cross sectional echocardiography can visualise a ventricular septal defect only if the defect size is more than the resolution of the ultrasound scanner (normally approximately 2 mm). Problems in diagnosis are, however, compounded if the defect is located in the trabecular septum or there are multiple defects. In trying to overcome these difficulties, an approach allowing the direct visualisation of blood flow across the ventricular septum seems ideal. Until now, demonstration of trans-septal flow in small ventricular septal defects could be reliably achieved only by cardiac catheterisation and angiocardiology. Nevertheless, invasive techniques carry a significant risk of morbidity and mortality, and clearly a reliable non-invasive alternative would be preferable. Several non-invasive Doppler techniques for detecting ventricular septal defects have been reported.⁷⁻¹³ Jugular venous continuous wave Doppler techniques are unreliable particularly with smaller defects, and there are also several disadvantages of methods using standard pulsed Doppler ultrasound. Using this technique, Magherini *et al* were unable to localise defects in the inlet portion and found ventricular septal defects difficult to detect if the shunt was balanced as in pulmonary hypertension.¹¹ Furthermore, ventricular septal defects could not be differentiated from right ventricular outflow tract obstruction. When a small pulsed Doppler sample volume is used as a roving interrogator of flow within the ventricular cavities and septum, it is never certain whether absence of detected systolic turbulence means that there is no defect or that a jet has been missed. The colour Doppler technique differs from previous approaches in that flow within an entire echocardiographic cross sectional cut of the heart is simultaneously displayed, thus minimising the possibility of missing the blood flow jet of a ventricular septal defect. Furthermore, the diagnosis is based on a combination of blood flow turbulence, direction, and timing.

In the present study, we found that using the colour Doppler technique the presence of trans-septal blood flow was clearly demonstrated in every patient with a ventricular septal defect. Furthermore, the technique permitted detection and localisation of ventricular septal defects in patients whose defects were too small to be visualised by standard cross sectional echocardiography. The recent findings of Miyatake *et al*⁵ concur with this result. Using a short axis view in a patient with a small ventricular septal defect they also found that colour Doppler images clearly demonstrated the flow disturbance even though conventional cross sectional echocardiography was unable to detect the defect. Though our study was not designed to determine accurately the specificity and sensitivity of

the method, both are clearly superior to standard cross sectional echocardiography. The technique also proved of use in the case of multiple ventricular defects by simultaneous demonstration of more than one flow jet. Similarly, it was shown to be useful in demonstrating the presence or absence of any residual ventricular septal defect in patients after primary surgical closure. The need to look serially for the presence of residual ventricular septal defects in patients in the immediate postoperative period has been shown by Stevenson *et al*.¹⁴ Immediately after surgery they found a 93% incidence of residual shunts, a value which decreased progressively over the ensuing days. It seems likely that the colour Doppler technique will be able to simplify the initial detection, localisation, and serial monitoring of these residual defects.

Many of the patients in this study had heart rates of over 100 beats/minute. In all patients, but particularly in these, it was necessary to review blood flow information in slow motion in order definitively to locate trans-septal flow in the right ventricle in systole. This is because in most patients, using an apical four chamber view, the trans-septal blood flow jet was predominantly towards the transducer. Since diastolic inflow is in the same direction it also produced a similar colour Doppler appearance within the right ventricle. Thus, by replaying the colour Doppler recording in slow or stopped motion, the transseptal blood flow jet depicted in blue could be seen frozen against a red background of ventricular ejection. In the same stopped frame, systole could be confirmed by a Doppler shift to the red within the left ventricular outflow tract. Thus any confusion with diastolic inflow that could occur in real time was easily avoided.

We conclude that direct visualisation of trans-septal blood flow by colour Doppler is reliable and reproducible and will provide clinical help in excluding ventricular septal defects in patients with innocent murmurs and in those whose ventricular septal defects are thought to have been surgically closed. Most importantly, the technique permits accurate localisation of defects that are otherwise invisible to cross sectional echocardiography. Since there is increasing evidence of the key role of the site of the defect to its natural history and probability of spontaneous closure,¹⁵ the method should in the future help in providing more accurate prognostic information for the individual patient.

FJM and RKH are supported by the Vandervell and British Heart Foundations. This work was supported in part by the Child Health Research Appeal Trust.

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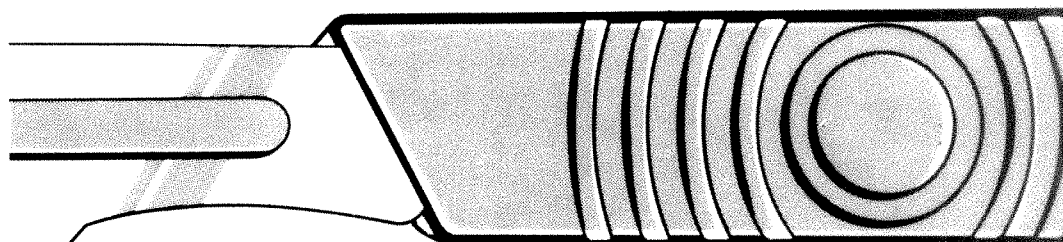
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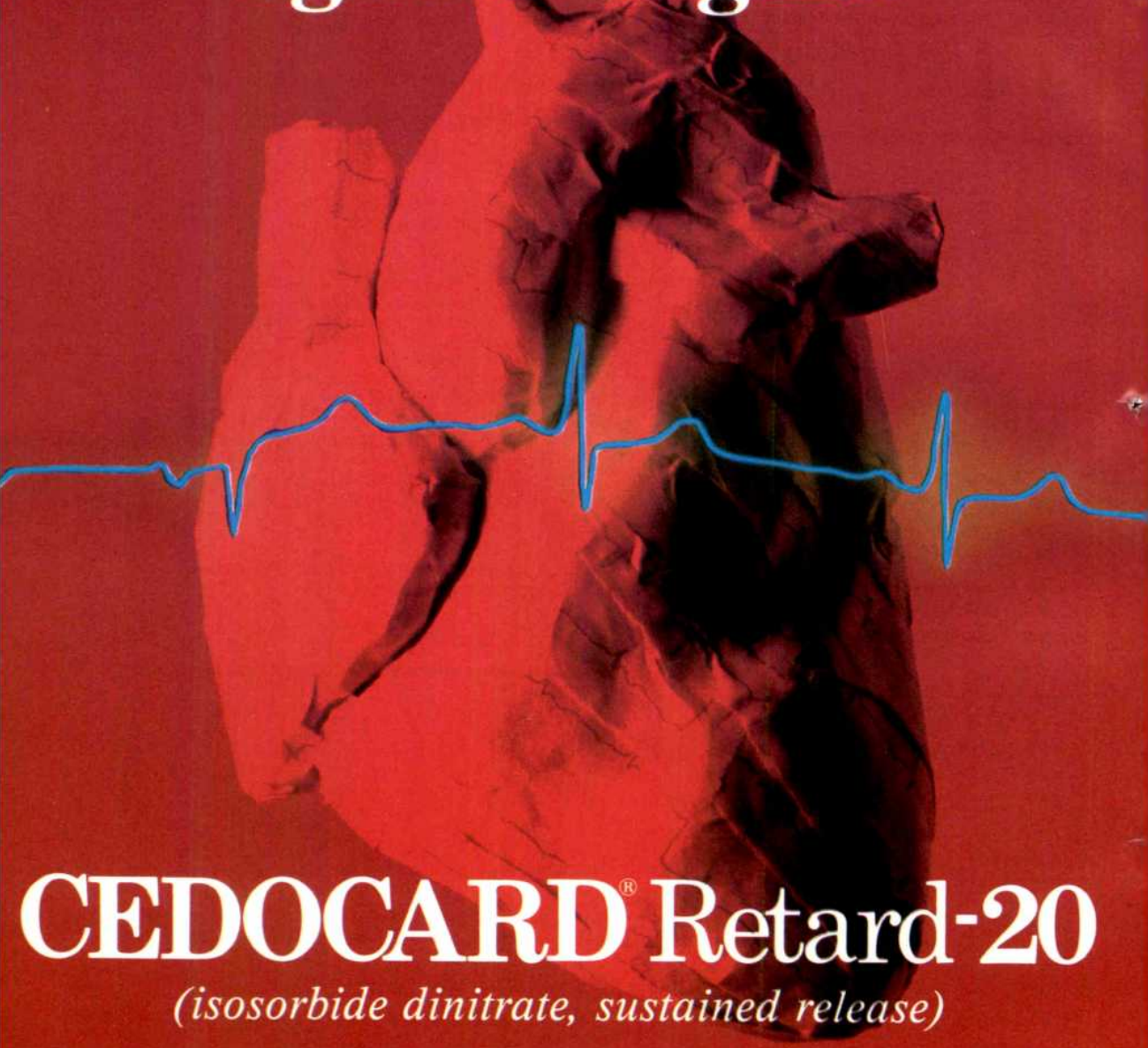
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Cross sectional echocardiographic and angiocardigraphic correlation in criss cross hearts

PETER J ROBINSON, VACHERA KUMPENG, FERGUS J MACARTNEY

From the Hospital for Sick Children, London

SUMMARY Cross sectional echocardiography can provide accurate anatomical diagnosis in congenital heart diseases and therefore should be able reliably to identify criss cross hearts and enable the analysis of their sequential arrangement non-invasively. The cross sectional echocardiographic diagnoses in eight consecutive patients with this condition were compared with those made at cardiac catheterisation and cineangiocardigraphy (five retrospectively, three prospectively). The mean number of invasive studies required to reach the diagnosis was 1.9 (range 1-4). Complete anatomical diagnosis was achieved with cross sectional echocardiography in all patients, but identification of ventricular morphology was much more straightforward using cineangiocardigraphy. If the transducer was held steady in either a precordial or subcostal position and rocked anteriorly and posteriorly the characteristic crossing over of the ventricular inflows could easily be seen. In no plane was there normal parallel arrangement of ventricular inflows.

A complete diagnosis should be possible in these patients using cross sectional echocardiography in experienced hands and at a single session in the cardiac catheterisation laboratory.

Criss cross heart is a rare rotational abnormality of the heart in which systemic and pulmonary venous streams cross without mixing at atrioventricular valve level.¹ As this definition suggests, it is an abnormality of relation rather than connection² but is often associated with abnormalities of connection, and usually accompanies other complex intracardiac anomalies.³⁻⁸ The ventricles are most often arranged in a relatively superoinferior fashion with the right sided atrium connecting with the left sided ventricle, and the left sided atrium with the right sided ventricle. Establishment of the precise type and mode of atrioventricular connection may not be achieved unless multiple angiocardigrams, with varying projections and sites of injection, are used. Thus repeated cardiac catheterisations may be required before the precise diagnosis is established.⁴

A single case report of the cross sectional echocardiographic diagnosis of criss cross heart has recently been published.⁹ To assess the relative roles of cross sectional echocardiography and angiocardigraphy in this condition we reviewed the cases seen at this hospital since 1980 and compared our cross sectional

echocardiographic diagnoses with the findings at cardiac catheterisation and angiocardigraphy.

Patients and methods

Eight patients with this condition have been seen since January 1980 (four male, four female) aged 6 weeks to 12 years (median 3.5 years) at initial presentation. Cross sectional echocardiography, cardiac catheterisation, and cineangiocardigraphic records were retrospectively reviewed in five patients. Three further patients were examined prospectively during the time of the study using our standard echocardiographic protocol.¹⁰

Cardiac catheterisation was performed using standard techniques with 1-4 (mean 1.9) studies required per patient before a definitive diagnosis was made. In all patients recognition of the criss cross had been assisted either by right atrial or caval injections or by follow through opacification of the left atrium and ventricle. Cross sectional echocardiographic studies were performed with an ATL (Advanced Technology Laboratory) Mark V mechanical sector scanner and a 3 or 5 MHz transducer in four patients, a Toshiba SSH 20 system with a 2.5 MHz transducer in one patient, and an ADR 4000S mechanical sector scanner with a 3 MHz transducer in the last three patients. The resulting videotapes were reviewed. Echocar-

Requests for reprint to Professor F J Macartney, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Accepted for publication 5 March 1985

Table *Invasive and non-invasive findings*

Case No	Age	Sex	Cross sectional echocardiography							
			Situs	AV connection	RAVV	LAVV	VSD	RVOTO	VA connection	Gt vessel position
1	5 mnth	M	Solitus	C	N	N	Perimembranous inlet outlet	Valvar, subvalvar	D	Ao anterior and I
2	4 yr	F	Solitus	C	N	S	Perimembranous inlet outlet	—	C	Ao anterior and I
3	5 yr	M	Solitus	C	N	N	Trabecular inlet	Subvalvar	D	Side by side, Ao L
4	6 wk	F	Solitus	C	N	S	Perimembranous inlet	—	D	Ao anterior and I
5	1 yr	M	Solitus	C	N	N	Perimembranous inlet outlet	—	D	Ao anterior and I
6	3 yr	F	Solitus	D	N	N	Perimembranous inlet outlet	—	DORV	Ao anterior and I
7	12 yr	F	Solitus	C	N	N	Perimembranous inlet outlet	—	C	Ao anterior and I
8	10 yr	M	Solitus	C	N	S	Perimembranous inlet outlet	—	C	Ao posterior and I

—, absent; Ao, aorta; AV, atrioventricular; C, concordance; D, discordance; DORV, double outlet right ventricle; Gt vessel position, great vessel position in relation to each other; L, left; LAVV, left atrioventricular valve; N, normal; O, override; R, right; RAVV, right atrioventricular valve; RVOTO, right ventricular outflow tract obstruction; S, stenotic; VA, ventriculoarterial; VSD, ventricular septal defect.

diographic and angiocardigraphic opinions were reached by consensus between us. Two patients died; in one the heart was available for detailed necropsy.

Results (Table)

CROSS SECTIONAL ECHOCARDIOGRAPHY

Each patient had situs solitus of the atria as shown by a left sided aorta and right sided inferior vena cava draining to the right atrium in subcostal cuts.¹¹ Con-

cordant atrioventricular connections were present in seven patients and discordant atrioventricular connections in one. In each case it was impossible to find a plane showing simultaneous and parallel arrangement of the atrioventricular valves and ventricular inflow regions, as described by van Mill *et al.*⁹ A more definitive criterion, in our opinion, was the direct demonstration of a criss cross atrioventricular relation. This could be obtained by positioning the transducer in such a way as to demonstrate from

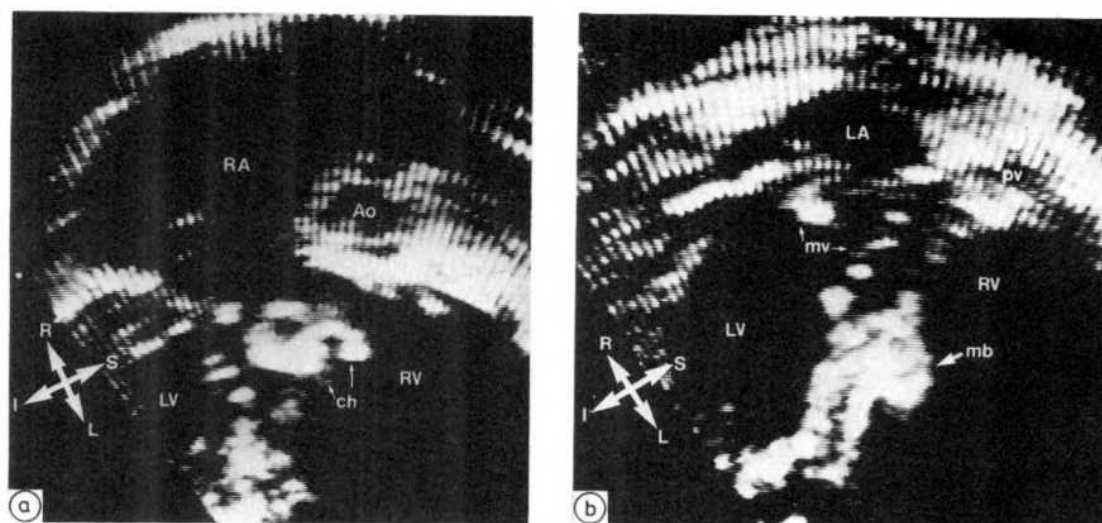


Fig. 1 Cross sectional echocardiograms from the apex (a) shows connection of the right atrium (RA) to the right ventricle (RV) with the aortic root (Ao) cut in its short axis. The right (RV) and left ventricles (LV) are in superoinferior arrangement and the tricuspid valve has a bright echo on the septal leaflet (see text). (b) shows, from the same transducer position at the apex but with more posterior angulation, a pulmonary vein (pv) draining to the left atrium (LA) which is connected to the left ventricle (LV). The mitral valve (mv) opens across the plane of right ventricular inflow (see (a)). Note the moderator band (mb) in the right ventricle. I, inferior; L, left; R, right; S, superior; ch, chordae.

Cardiac catheterisation

Situs	AV connection	RAVV	LAVV	VSD	RVOTO	VA concordance	Gt vessel position
Solitus	C	N	N	Perimembranous	Valvar, subvalvar	D	Ao anterior and L
Solitus	C	N	S	Perimembranous	—	C	Ao anterior and L
Solitus	C	N	N	Perimembranous	Valvar, subvalvar	D	Side by side, Ao to L
Solitus	C	N	S	Perimembranous	—	D	Ao anterior and L
Solitus	C	N	N	Perimembranous	—	D	Ao anterior and L
Solitus	D	N	N	Perimembranous outlet	—	?DORV	Ao anterior and L
Solitus	C	O	N	Perimembranous	—	C	Ao anterior and L
Solitus	C	N	S	Perimembranous outlet	—	C	Ao posterior and R

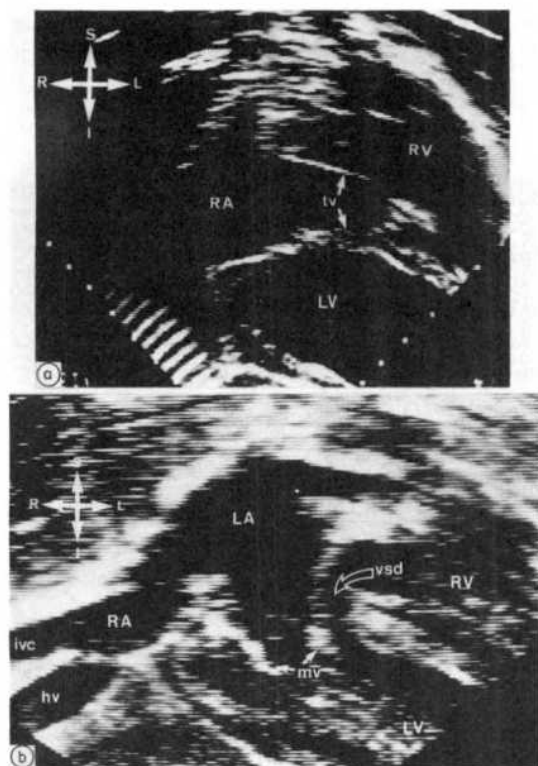


Fig. 2 Cross sectional echocardiograms from the same transducer position with more anterior angulation in (a) and more posterior angulation in (b) showing the criss cross arrangement of ventricular inflow region. hv, hepatic vein; I, inferior; ivc, inferior vena cava; L, left; LA, left atrium; mv, mitral valve; R, right; RA, right atrium; RV, right ventricle; S, superior; tv, tricuspid valve; vsd, ventricular septal defect.

below each atrium crossing to the contralateral ventricle, with one atrioventricular connection crossing behind the other (Figs. 1 and 2). The precise transducer position required varied from case to case in these highly complex hearts but was usually from the apex or subcostal region. One patient had a straddling tricuspid valve, but no patient had mitral straddling. Three patients, all with concordant atrioventricular connections, had cross sectional echocardiographic evidence of stenosis of the mitral valve (Fig. 3), and one showed a mobile bright echo on the septal leaflet

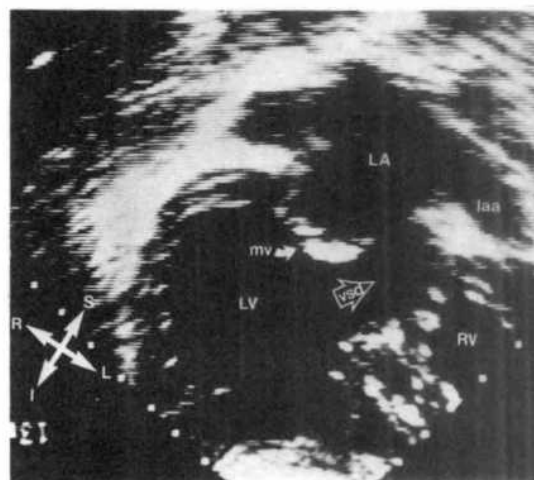


Fig. 3 Cross sectional echocardiogram from the apex showing doming of the stenosed mitral valve (mv) in a patient with a criss cross heart. I, inferior; L, left; LA, left atrium; laa, left atrial appendage; mv, mitral valve; R, right; RV, right ventricle; S, superior; vsd, ventricular septal defect.

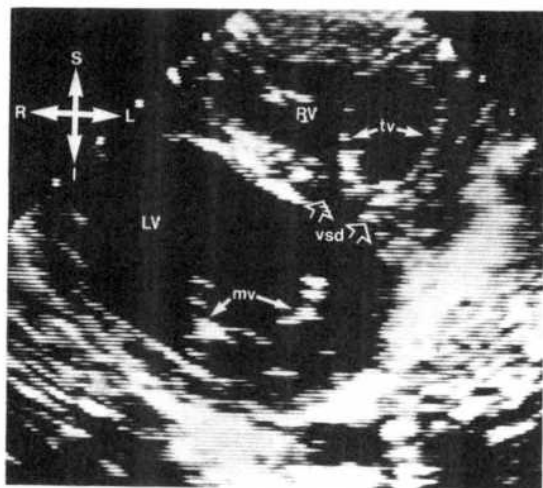
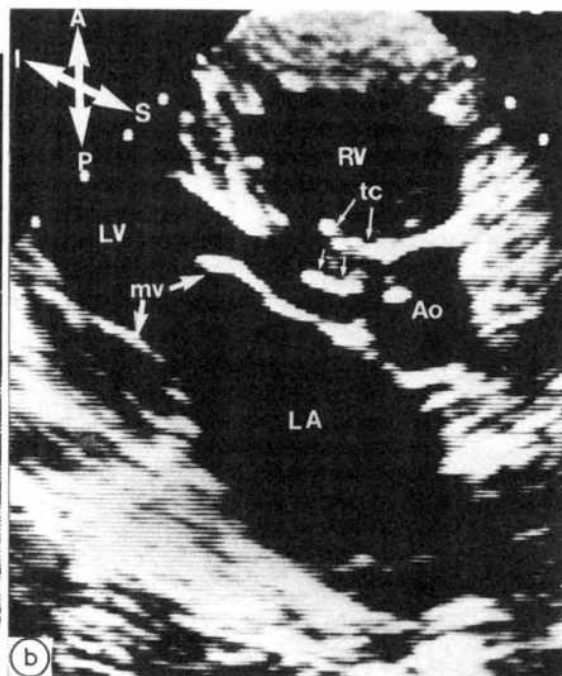
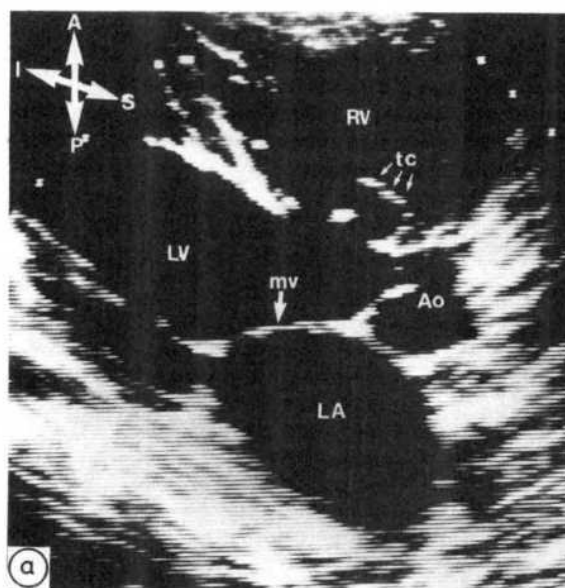


Fig. 4 Cross sectional echocardiogram showing the relative positions of the right (RV) and left ventricles (LV) with left ventricle inferior and slightly rightward of the right ventricle. Note the fishmouth appearance of the mitral valve (mv) and septal attachment of the tricuspid valve (tv). I, inferior; L, left; R, right; S, superior; vsd, ventricular septal defect.

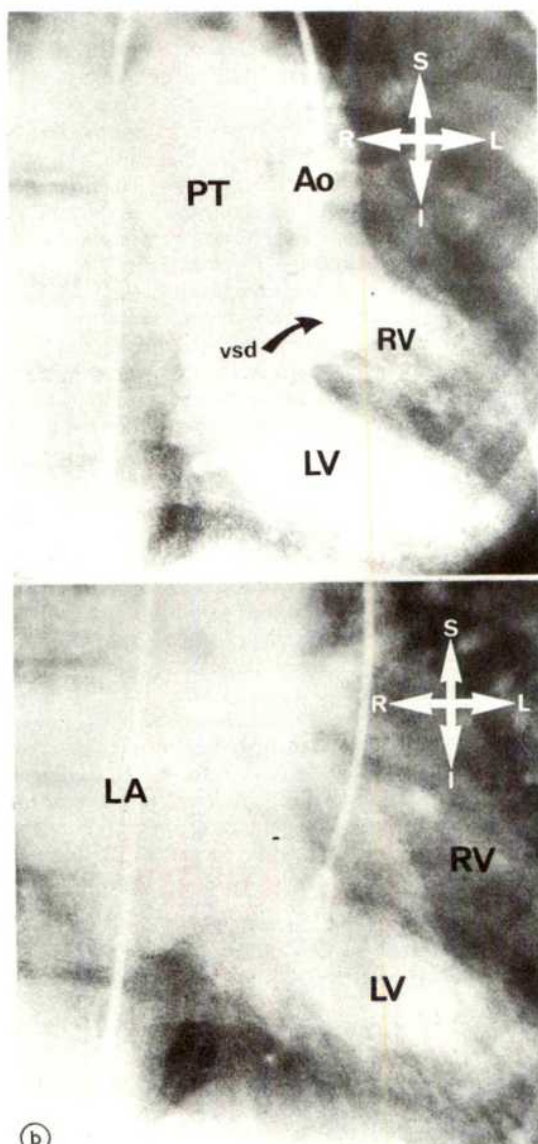
of the tricuspid valve (Fig. 4). This echo was very similar to one seen in another patient that proved at operation to be ruptured chordae tendineae that had coiled back on themselves.

Because we were uncertain of the precise transducer position used in retrospective studies the cross sectional echocardiographic determination of relative ventricular position was usually not possible retrospectively. In the three patients studied prospectively before angiocardigraphy (Fig. 5), however, the ventricular positions were correctly predicted as right ventricle slightly anterior, superior, and leftward and left ventricle slightly posterior, inferior, and rightward.

As all our patients had ventricular septal defects that extended to the inlet portion of the septum we could not use offsetting of the atrioventricular valves to identify ventricular morphology. We therefore used either the moderator band as a marker of right ventricle or the fishmouth appearance of the mitral valve in short axis cuts to identify a left ventricle (Figs. 1b and 4). The ventricular septal defect extended through the perimembranous region to the muscular outlet region in five patients and was subaortic in two. In one patient tricuspid tissue protruded through the



Figs. 5(a) and (b) Long axis cross sectional echocardiograms showing tricuspid valve (tc) tissue prolapsing into the right ventricle (RV) in systole and into the left ventricular (LV) outflow tract in diastole. A, anterior; Ao, aortic root; I, inferior; LA, left atrium; mv, mitral valve; P, posterior; S, superior.



(b) Figs. 6(a) and (b) Anteroposterior cineangiograms from an injection into the left ventricle (LV) with follow through left atrial (LA) opacification in a patient with criss cross heart, atrioventricular concordance, and ventriculoarterial discordance. Ao, aorta; I, inferior; L, left; PT, pulmonary trunk; R, right; RV, right ventricle; S, superior; vsd, ventricular septal defect.

ventricular septal defect to the left ventricular outflow tract in diastole and into the right ventricle in systole (Fig. 5). No patient had subaortic obstruction. Two had subpulmonary obstruction due to fibromuscular tunnel formation, one with associated valvar stenosis.

The origin of the great arteries from the ventricles

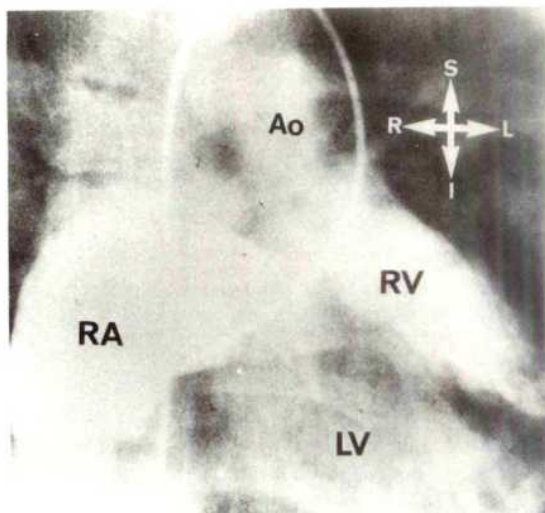


Fig. 7 Cineangiogram from the same patient as in Figs. 6(a) and (b), with injection into the right atrium. The projection is anteroposterior and comparison with Figure 6(b) shows the criss cross arrangement of ventricular inflow regions. Ao, aorta; I, inferior; L, left; LV, left ventricle; R, right; RA, right atrium; RV, right ventricle; S, superior.

was easily recognised by echocardiography. There were concordant ventriculoarterial connections in three patients, two with the aorta anterior and slightly leftward of the pulmonary trunk and one with the usual great vessel relation. One patient had double outlet right ventricle with the aorta anterior and slightly to the left of the pulmonary trunk, and four patients had discordant ventriculoarterial connections, three with aorta anterior and to the left of the pulmonary trunk and one with side by side great vessels with aorta to the left. In the three patients studied prospectively the aortic arch was left sided and a persistent ductus arteriosus was excluded.

HAEMODYNAMICS AND ANGIOCARDIOGRAPHY (Figs. 6 and 7)

Atrial situs, atrioventricular and ventriculoarterial connections were confirmed by angiocardiology in all patients. (Cineangiocardiology showed the criss cross arrangement when appropriate sites of injection were used.) Pressure measurements confirmed the presence of mitral stenosis in the correct three patients and excluded atrioventricular valve stenosis in the others. Subpulmonary stenosis was confirmed by pressure measurements in one patient and angiocardiology in the other. Though there were no mistakes with echocardiography, ventricular morphology was more obvious on angiocardiology than on cross sectional echocardiograms. Precise localisa-

tion of the ventricular septal defect was not always possible with certainty angiocardigraphically because of problems in profiling the plane of the interventricular septum.^{10,12} Likewise atrioventricular valve straddling was better appreciated echocardiographically.¹³ The aortic arch was left sided and a persistent ductus arteriosus was excluded in all patients.

NECROPSY FINDINGS

Necropsy confirmed the premortem diagnoses and found no new abnormalities.

Discussion

This study shows how the systematic cross sectional echocardiographic examination of hearts with criss cross arrangement of their inflow portions can provide accurate anatomical information and highlights how well suited this technique is to the segmental approach in the diagnosis of complex congenital heart disease. In criss cross heart both ventricles and great vessels may be in unexpected positions, but a careful systematic approach will demonstrate the connections, particularly if continuous sweeps between routinely used cross sectional echocardiographic cuts are used. This was exemplified in our study particularly in one patient in whom the aorta was almost directly anterior to the pulmonary trunk and yet the great vessels connected in concordant fashion.

There has previously been only one case report showing the ability of cross sectional echocardiography to make a nearly complete anatomical diagnosis in this condition. Those authors used subcostal cuts alone, parasternal cuts having been unsuccessful.⁹ While we agree that much of the anatomical information may be obtained from these cuts, we found that the precordial views were useful in confirming the impressions gained from the subcostal cuts. Furthermore, precordial cuts were superior in identifying subpulmonary obstruction, great vessel position, and in some cases the actual recognition of the criss cross arrangement of the atrioventricular junction. A further disadvantage of relying on subcostal cuts is that they may not provide a plane showing opening of both atrioventricular valves. If the transducer is not angled sufficiently either anteriorly or posteriorly a false impression of either double inlet ventricle or absent atrioventricular connection may be given, as in the initial echocardiographic diagnosis of the patient studied by van Mill and colleagues.⁹ Although we agree that the normal parallel arrangement of the right ventricular and left ventricular inflow tract is not seen in this condition, we have shown how the actual demonstration of the criss cross arrangement is possible echocardiographically.

In understanding the underlying anatomy of hearts with normal and criss cross atrioventricular relations it is helpful to think of atrioventricular channels running from each atrium to the inlet and apex of the ventricle to which it is connected. In normal hearts these two channels are roughly parallel, with the result that it is possible to obtain a four chamber section of the heart in which each atrium is connected to the ipsilateral ventricle and the atrioventricular valves open in the same direction. By contrast, in criss cross hearts the atrioventricular channels cross one another with the result that the atrioventricular valves open in different directions, and views can be obtained in which one or other atrium connects to the contralateral ventricle as seen in the echocardiographic section. This may well not correspond to the conventional frontal, sagittal, or horizontal plane of the body. When the atrioventricular connection is biventricular, one atrioventricular channel must cross in front of the other. This means that it is impossible to demonstrate the entire criss cross in a single tomographic section.

Thus cross sectional echocardiography performed systematically and following a preset routine by experienced operators should allow complete sequential anatomical diagnosis of these complicated hearts non-invasively. Cardiac catheterisation can be planned much more precisely and should be needed only for gaining pressure and oximetric data and to rule out additional ventricular septal defects. A complete anatomical and physiological diagnosis should now be possible in these patients using cross sectional echocardiography and a single session in the cardiac catheterisation laboratory.

PJR was supported by the Wellcome Foundation and FJM is supported by the Vandervell and British Heart Foundations.

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Evaluation of an elliptical area technique for calculating mitral blood flow by Doppler echocardiography

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SUMMARY To evaluate a method for measuring blood flow through the mitral valve 18 normal subjects and 19 patients with cardiac disease in whom mitral and aortic blood flows were identical were studied. Initially the mitral ring area was planimetered from the echocardiographic image, but the results of area calculation using the mathematical formula for the area of an ellipse were found to approximate to within 8% of the planimetered result in most cases. The formula was therefore used if the ring appeared elliptical on the cross sectional echo image, and other shapes were planimetered. Mitral velocity, aligned with flow in three planes, was recorded just distal to the ring. Mitral flow calculated using the elliptical technique correlated closely with flow measured in the ascending aorta by the Doppler technique and also with systemic flow measured by the Fick method at cardiac catheterisation in 10 patients.

The mitral flow technique that assumed a circular orifice correlated almost as well with Doppler aortic flow and with Fick flow but overestimated flow by a mean of 1446 ml, whereas the elliptical method had a mean error of only 138 ml. Both methods correlated well with standards, but the elliptical method was easy to apply and gave a better correlation with comparison reference values.

Calculation of flow by the Doppler method requires measurement of the mean velocity of flow, the intercept angle (theta) between the measurement axis and the direction of flow, and the area of the orifice or conduit through which flow is passing. This concept can be expressed as follows: $\text{flow} = (\text{mean velocity} \times \text{area}) / \cos \theta$.

In theory the combination of cross sectional imaging and Doppler echocardiography permits measurement of all these variables, and all the information necessary for flow calculation can be obtained from these methods. The reliability of data from various possible flow measurement sites has been the subject of many investigations. Measurement of aortic,¹⁻³ pulmonary,^{2,4,5} and tricuspid⁶ blood flow by Doppler echocardiography has been found to be accurate when compared with reference standards. Mitral flow has presented a more difficult problem. The measurement of mitral velocity is relatively simple, but the determination of the area through which flow is passing is much more difficult. Two methods have been used.

The first method required imaging the maximal mitral leaflet orifice in short axis and altering that area by a factor derived from measurements of the mitral complex on an M mode recording.⁷ Although this method provided accurate flow measurements in dogs, in humans the correlation with flows measured by other methods was poor.⁶ This discrepancy was probably related to the different shape of the mitral orifice in the two species. Reports have been published of an alternative method that treats the mitral orifice as a circle.^{8,9} This method appears to improve the correlation, but further assessment is needed.

We report a method that provides a more accurate estimate of the area of the mitral orifice and provides a better correlation with reference standards.

Patients and methods

The study population consisted of 18 normal subjects (aged 3 to 35 years) and 19 children (aged from infancy to 17 years) with a variety of congenital cardiac malformations (Table 1). The selection of patients was determined mainly by the nature of their cardiac lesion. Patients were included if their aortic and mitral flows would be expected to be equal on the

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Accepted for publication 19 February 1985

Table 1 Patient data, mitral valve dimensions, and mitral flow velocities by the various methods

Case No	Diagnosis	Mitral valve dimension (cm)	Ratio*	Mitral flow (ml/min)		Aortic flow† (ml/min)	Fick flow (ml/min)
				Ellipse	Circle		
1	Normal heart	3.85×2.07	0.54	3764	7005	3502	—
2	Normal heart	4.32×2.96	0.69	6263	9164	7915	—
3	Normal heart	2.10×1.22	0.58	2007	3458	2217	—
4	Atrial septal defect	3.20×2.60	0.81	4545	5597	5658	—
5	Normal heart	2.37×1.73	0.73	3279	4494	3339	—
6	Normal heart	2.43×2.43	1.00	5238	5238	6224	—
7	Normal heart	3.20×1.80	0.57	4192	7455	4502	—
8	Normal heart	3.50×2.18	0.62	5498	8832	5817	—
9	Normal heart	2.00×1.47	0.74	3461	4712	2810	—
10	Normal heart	1.85×1.44	0.78	2123	2725	2611	—
11	Normal heart	1.60×1.20	0.75	1275	1700	1132	—
12	Persistent ductus arteriosus	2.50×2.02	0.80	4234	5242	3707	—
13	Supraventricular tachycardia	2.30×1.56	0.67	5526	8151	6623	—
14	Normal heart	2.80×2.20	0.79	4369	5564	4663	—
15	Normal heart	4.10×2.90	0.71	7554	10614	7590	—
16	Aortic stenosis	3.50×2.93	0.84	9867	11793	9923	—
17	Postoperative tetralogy of Fallot or ventricular septal defect	3.25×2.40	0.74	4507	6107	4375	—
18	Normal heart	2.80×2.00	0.71	4414	6188	5288	—
19	Normal heart	3.40×2.80	0.82	5945	7223	4905	—
20	Normal heart	2.80×2.00	0.71	5621	7887	4727	—
21	Normal heart	3.00×2.40	0.80	6850	8567	7002	—
22	Normal heart	3.10×2.40	0.77	4450	5751	5359	—
23	Normal heart	2.90×2.20	0.75	6881	9075	6509	—
24	Persistent ductus arteriosus	3.10×2.22	0.72	6089	8486	6615	6400
25	Persistent ductus arteriosus	1.60×1.20	0.75	2437	3245	2796	—
26	Atrial septal defect	2.90×2.20	0.76	3426	4517	3279	3300
27	Pulmonary stenosis	1.90×1.50	0.79	2160	3481	2280	2400
28	Pulmonary stenosis	2.80×2.20	0.79	3438	4317	3213	3200
29	Atrial septal defect	2.55×1.85	0.73	3749	5025	3739	3600
30	Atrial septal defect	2.75×2.20	0.80	2830	3538	3160	—
31	Atrial septal defect	4.00×3.01	0.75	5479	7309	5547	—
32	Postoperative tetralogy of Fallot or ventricular septal defect	1.60×1.25	0.78	1241	1625	1372	—
33	Aortic stenosis	Irregular	—	3349‡	5661§	3160(T)	3000
34	Atrial septal defect	2.40×1.80	0.75	3738	4983	3832	3400
35	Pulmonary stenosis	1.47×1.07	0.73	1241	1341	1372	1100
36	Aortic stenosis	Irregular	—	2430‡	¶	2200(T)	2300
37	Postoperative tetralogy of Fallot or ventricular septal defect	2.45×1.40	0.57	3050	5381	2670	1400

*Ratio of minor to major axis of the mitral valve.

†(T), flow measured at the tricuspid valve.

‡Area determined by planimetry.

§Value calculated from a diameter measurement.

¶Incalculable because of lack of satisfactory diameter measurement.

basis of their known cardiac malformation. Patients with abnormal mitral valves (mitral stenosis or atrioventricular defects) were excluded as were patients with significant aortic stenosis or incompetence. In 10 patients mitral flow was measured simultaneously by the Fick method and by the Doppler technique during cardiac catheterisation.

AORTIC FLOW MEASUREMENT

Aortic flow measured by the Doppler technique or systemic flow measured by the Fick method served as reference standards for mitral flow measured by the

Doppler technique. Aortic flow was measured as previously described.² An off axis imaging transducer was placed in the suprasternal notch and the cursor aligned with the walls of the mid-ascending aorta. The highest velocity with the least spectral broadening was obtained by manipulation of the transducer within the two visualised planes. The transducer was then moved carefully in the third plane to maximise velocity and reduce spectral broadening. When this manoeuvre was completed the velocity obtained was considered to be the true maximal velocity, and no correction for an intercept angle was used. This same

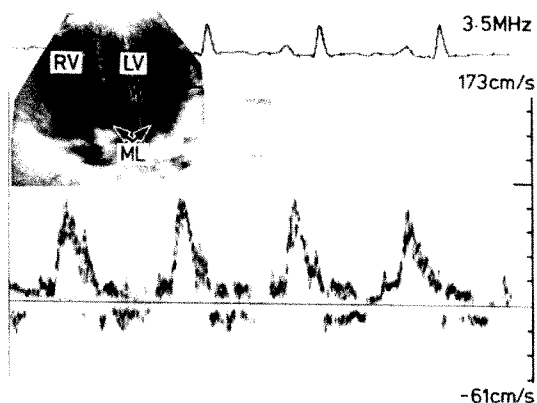


Fig. 1 Mitral velocity tracing and a cross sectional echocardiogram showing the site from which it was recorded. The cursor is shown as a highlighted imaging line and the sample volume as two parallel lines flanking the cursor. RV, right ventricle; LV, left ventricle; ML, mitral leaflets.

spatial alignment technique was used for velocity recordings at all other sites. The aortic diameter was measured at the level of the centre of the sample volume by lateral resolution (centre of the brightest portion of the image of one wall to a similar point on the other wall) from the same transducer location in the suprasternal notch and was then converted to an area using the formula: $\text{area} = 3.1416 \times (\text{diameter} \times 0.5)$ squared.

TRICUSPID FLOW MEASUREMENT

Tricuspid flow was measured as previously described.⁶ From an apical four chamber imaging plane, a spatially aligned velocity was obtained just distal to the tricuspid ring. The tricuspid orifice diameter was measured between the insertions of the valve leaflets on to the ring and the diameter was converted to an area by applying the same formula as for the aorta.

MITRAL FLOW MEASUREMENT

Mitral velocity was recorded from the apical four chamber imaging plane by placing the sample volume just distal to the ring and generally aligned with the septum. The optimal transducer location was one that placed the septum vertically within the imaging cone (Fig. 1) or one in which the apical septum tilted slightly to the right. The sample volume was located approximately at the leaflet commissure. A site with large amplitude negative velocities (from the left ventricular outflow tract) was avoided. The ultrasound beam was then spatially aligned with flow as previously described to record the maximal velocity, an example of which is shown in Fig. 1. Mean velocity was determined by manually digitising the modal vel-

ocity of at least three cardiac cycles on a digitising pad interfaced to an Apple II computer. The modal velocity is the most commonly occurring velocity at any given instant and appears therefore as the blackest part of the time-velocity trace (Fig. 1). The computer, which was controlled by a dedicated Biodata program, was used to determine the area enclosed by the time-velocity curve and to calculate mean velocity per second by dividing this area by the distance along the horizontal axis. This process has been described in detail.¹⁰ To measure the mitral ring diameter the transducer was placed in the parasternal short axis plane, and the root of the aorta, including the cusps, was imaged. The transducer was then angled slightly inferiorly and leftward to image the mitral ring. The ring was usually elliptical, but sometimes the posterior right area was slightly flattened.

The valve rings were photographed from a video tape recording. Although the ring size did not change much with the cardiac cycle it was considerably easier to measure in early diastole because the leaflet tissue was displaced into the ventricle. The axes were measured from the monitor using a manual caliper, and then that distance was measured with electronic calipers. This method provided increased accuracy and control compared with primary measurement with electrical calipers. The major axis was measured by lateral resolution and the minor axis by the leading edge technique. The major axis measurement provided data essentially the same as measurement of the ring orifice from the four chamber plane, and this value was used for the calculation of mitral valve area by the circle method.

Initially, images were recorded of 20 such orifices and the area determined by planimetry. The results were compared with those of the area calculated according to the formula: $\text{area} = a \times b \times 3.1416$, where a is the major axis and b the minor axis measured perpendicular to the mid-point of the major axis. The results of the area calculation were within 8% of the planimeted area if the ring was approximately an ellipse or a flattened ellipse. If the ring was scalloped or irregular, however, the calculated and planimeted areas differed by 10% to 20%. Therefore for this study all scalloped or irregular rings were planimeted and the area of all the regular rings was determined by the formula. In both instances the accepted value was the mean of at least three beats. The time required to obtain appropriate velocities and area measurements in a cooperative subject was 3–4 minutes.

STATISTICAL ANALYSIS

The results of the various measurements of mitral, aortic, and Fick blood flows were compared by linear regression analysis and paired t test.

Results

Data of adequate quality were obtained from all patients selected for study, and no imaging or velocity recording proved to be particularly difficult.

MITRAL RING SHAPE

The mitral rings were found to vary in shape. One normal subject and two patients had orifices that were clearly neither an ellipse nor a flattened ellipse. The normal subject had a ring that was essentially circular. The two patients had rings with significant scallops. The remainder had rings that were approximately elliptical or flattened ellipses. The range of the ratio of minor to major axis, excluding the subjects with the round or irregular orifices, was 0.54–0.84 (mean 0.73). Most subjects had a ratio near 0.75 (Table 1).

COMPARISON OF MITRAL AND AORTIC DOPPLER FLOW MEASUREMENTS

Aortic blood flow measured by Doppler was recorded in 35 subjects. Two others had turbulent flow in the aorta, and therefore, in these patients, since no shunts were present tricuspid flow measured by the Doppler technique was substituted for aortic flow (Table 1). Mean mitral flow by the elliptical technique for 37 patients was 4230 ml/min (Table 2), which was not significantly different from mean aortic flow (4368 ml/min). Mean mitral flow by the circular technique (36 patients), however, was 5874 ml/min, which was significantly greater ($p < 0.01$) than aortic flow (mean 4428 ml/min) in the same patients.

Comparison of mitral flow, calculated by the elliptical method, with aortic flow (including the two patients with tricuspid measurements) measured by the Doppler technique gave a correlation of 0.96; SEE 516 ml; slope 0.90; intercept 297 ml (Table 2, Fig. 2). Mitral flow calculated by the circle technique and compared with the same group showed a correlation of 0.91; SEE 1003 ml; slope 1.13; and intercept 868 ml (Table 2, Fig. 2).

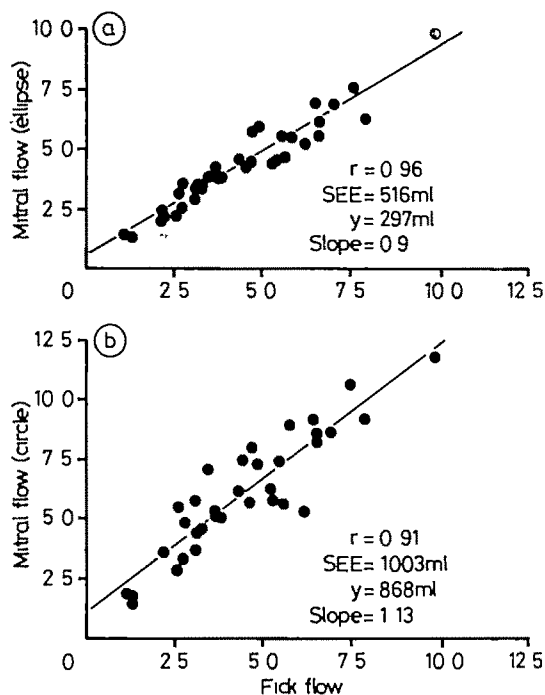


Fig. 2 Comparison of aortic flow (l/min) measured by the Doppler technique and mitral flow (l/min) measured by (a) the elliptical and (b) circular area techniques. r , correlation coefficient; SEE, standard error of the estimate; y , value of the intercept on the vertical axis.

COMPARISON OF DOPPLER AND INVASIVE FLOW MEASUREMENTS

Mean values for flow in 10 patients by the mitral elliptical (3267 ml/min), aortic (3236 ml/min), and Fick (3010 ml/min) methods were not significantly different (Table 2). The mean value for flow calculated by the mitral circular method in nine patients (4799 ml/min) was considerably greater than that by the Fick method in the same patients (mean

Table 2 Comparison and correlation of flow values through the mitral and aortic valves

Method	n	Mean (SD) (ml/min)	p	r	SEE (ml)	Slope	y axis intercept (ml)
Mitral flow (ellipse)	37	4230(1871)	NS	0.96	516	0.9	+ 297
Aortic flow	37	4368(1998)					
Mitral flow (circle)	36	5874(2465)	<0.01	0.91	1003	1.13	+ 868
Aortic flow	36	4428(1992)					
Mitral flow (ellipse)	10	3267(1271)	NS	0.93	435	0.81	+ 825
Fick flow	10	3010(1461)					
Mitral flow (circle)	9	4799(1896)	NS	0.82	1024	1.02	+1656
Fick flow	9	3088(1527)					
Aortic flow	10	3236(1407)	NS	0.96	370	0.93	+ 450
Fick flow	10	3010(1461)					

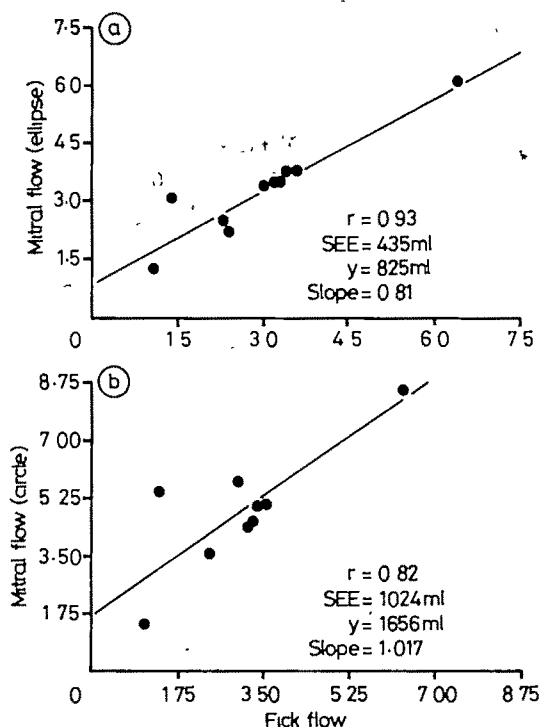


Fig. 3 Comparison of mitral flow measured simultaneously by the Fick method at catheterisation and by the Doppler technique with the mitral area calculated by (a) the elliptical and (b) the circular area methods. Abbreviations and calibration of axes as in Fig. 2.

3088 ml/min), but the difference was not statistically significant. The three Doppler flow measurements (mitral elliptical, mitral circular, and aortic) all correlated well with Fick flow (Figs. 3 and 4, Table 2) with

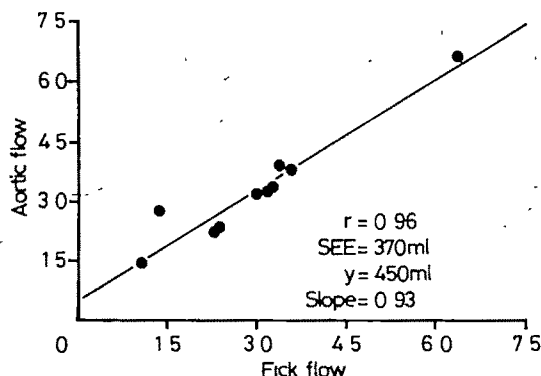


Fig. 4 Comparison of flow measured simultaneously at catheterisation by the Fick method and by the Doppler technique in the mid-ascending aorta. Abbreviations and calibration of axes as in Fig. 2.

correlation coefficients of between 0.82 and 0.96, the lowest correlation being for the comparison of the mitral circular method with Fick flow. Other descriptive statistics were different (Table 2). The standard errors of the estimate were: aortic (370 ml), mitral elliptical (435 ml), and mitral circular (1024 ml). The slope of the relation was very close to 1.0 for the mitral circular method but was significantly lower for the aortic and mitral elliptical techniques. The intercept was closest to the origin for aortic flow (+450 ml) and further for mitral elliptical (+825 ml) and mitral circular (+1656 ml).

Discussion

Three main findings emerge from this study: (a) mitral flow determined by either of the two evaluated techniques correlated reasonably closely with control flows, (b) mitral flow calculated by the elliptical orifice area technique provided a closer match with control flows than did mitral flow calculated by the circular area technique, (c) aortic flow measured by Doppler correlated closely with Fick flow and had the lowest standard error of the estimate of any of the Doppler measured flows.

MITRAL ELLIPTICAL TECHNIQUE

Brock observed that in the living patient the mitral annulus was not usually circular,¹¹ and careful assessment using cross sectional echocardiography confirms that, although the shape of the mitral annulus changes throughout the cardiac cycle, the orifice is essentially elliptical.¹² Anatomical studies have usually been performed by dividing the valve annulus and measuring the circumference rather than defining its precise shape. Rusted and colleagues showed that in a small number of adults the mean anteroposterior diameter of the mitral valve was 1.5 cm compared with an intercommissural diameter of 2.5 cm for men and of 2.1 cm for women.¹³ As they pointed out, however, the anteroposterior diameter could not be measured with the same degree of accuracy as the intercommissural diameter because of the way in which the valves had been opened. Figure 5 shows the shape of three typical mitral valve orifices, two in fresh postmortem specimens and one as seen from the parasternal short axis view using cross sectional echocardiography.

In most of the patients in the present study the orifice appeared to be a flattened ellipse, whereas in a few other patients it was irregular in shape containing angles or scallops (Table 1). Only one subject had a mitral orifice that was approximately circular. The valve ring was more difficult to image than the leaflets, but its shape and size were relatively constant throughout diastole whereas the leaflet orifice varied

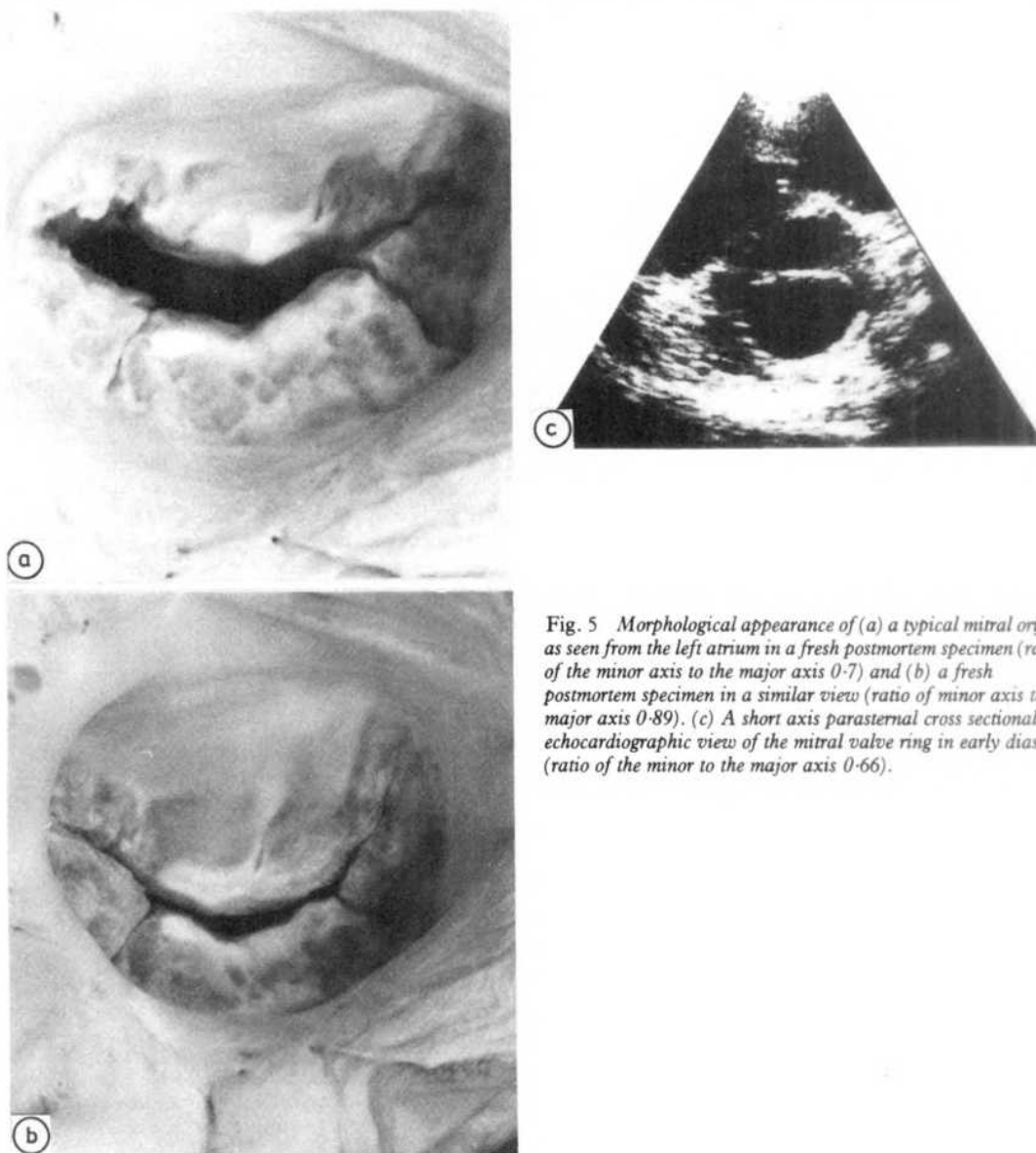


Fig. 5 Morphological appearance of (a) a typical mitral orifice as seen from the left atrium in a fresh postmortem specimen (ratio of the minor axis to the major axis 0.7) and (b) a fresh postmortem specimen in a similar view (ratio of minor axis to major axis 0.89). (c) A short axis parasternal cross sectional echocardiographic view of the mitral valve ring in early diastole (ratio of the minor to the major axis 0.66).

continuously. Essentially, the same shape and area can be measured from the leaflets near their insertion into the annulus, but this area constantly changes and equals or nearly equals the ring area only during early diastole. A true short axis image of the ring or the first portion of the leaflet is essential because imaging in any other plane might introduce angulation and foreshortening of one or the other of the axes.

MITRAL VELOCITIES

The correct cursor alignment needed to record maximal velocity with minimal spectral broadening of the signal may not parallel the septum, and the exact site must be determined by listening to the audiosignal and observing the monitor. Mitral velocity patterns are not identical from beat to beat and depend on cardiac cycle length and phase of respiration. There-

fore several cardiac cycles must be recorded and digitised.

PLANIMETRY VS ELLIPTICAL FORMULA

The elliptical formula for the mitral valve orifice area gave a value within 8% of the planimeted ring area when the ring was not scalloped or irregular in shape. The formula was used for its convenience and for economical reasons since printing several frames requires the use of expensive photographic paper. Nevertheless, since the mitral ring usually has the configuration of a slightly flattened ellipse planimetry is undoubtedly more accurate even for non-scalloped, regular bordered rings. Planimetry is mandatory for scalloped or irregularly shaped rings.

CORRELATION COEFFICIENTS

Correlations for comparison of all of the measurements in this study were high. The range of the data, however, was necessarily large because children of different ages were studied. A large range of values improves the correlation coefficient. If the range of values was reduced, as might occur in a study of an adult population, the same technique would be expected to have a lower correlation.

ERRONEOUS RESULTS WITH THE ELLIPTICAL METHOD

This method was not used in patients who had major mitral valve abnormalities such as atrioventricular defects or mitral stenosis. Furthermore, subjects who have the mitral valve in an unusual site may present a problem in proper alignment of the ultrasonic beam with the plane of the ring. This situation could lead to an underestimation of the area if one or other of the measurement axes was foreshortened. Finally, patients with calcification of the annulus may have increased reflections that might impede precise assessment of the valve ring dimensions.

COMPARISON OF THE THREE METHODS FOR MITRAL FLOW

Since all methods share the same velocity measurement the differences in calculated flows result from the differences in the way in which the flow area is calculated. The initial technique described by Fisher and associates⁷ provided a reasonably accurate assessment of mitral flow in dogs, but when data were compared with other techniques in humans the correlation coefficient with aortic flow was less than 0.6 and the standard error of the estimate exceeded 1 l/min.⁶ Preliminary results suggest that the circular area technique provides an improvement in both these respects.^{8,9} In the present study, however, the circular method consistently overestimated mitral flow because the orifice was rarely a full circle. This finding

is in contrast to the observation of Lewis and colleagues.⁹ Although the slope of the regression line of mitral flow by the circular method against Doppler aortic flow was almost as close to 1.0 as the slope of the regression line for the elliptical method, the standard error of the estimate was considerably larger and the intercept on the y axis was 868 ml (Fig. 2, Table 2). Therefore, over the range of flows measured in this study the circular method consistently overestimated mitral flow to a considerable degree. By comparison, the elliptical method, with a smaller positive intercept on the y axis and a correlation coefficient of 0.9, provided a better match of flows.

In favour of the circular area method is its simplicity since only one diameter measurement is required. A slight error in diameter measurement will, however, lead to a large error in calculated area because the radius is squared. In the present study the elliptical area method provided the better statistical results with values that could be applied directly with acceptable accuracy without calculating a correction based on the equation for the regression line. A correction would be required for the circular technique. The elliptical method makes fewer assumptions about the ring shape, and a small error in the measurement of one of the axes is less critical. The elliptical method is, however, slightly more difficult to apply. Two axes must be measured from video tape replay and any shape irregularity requires planimetry. The data show that, although both the circular and elliptical mitral area techniques have clinical value, the best results are found for mitral flow with the elliptical area measurement method.

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Functionless retained pacing leads in the cardiovascular system

A complication of pacemaker treatment

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SUMMARY Twenty one patients with retained endocardial pacemaker leads were followed during a total observation period of 1097 months to assess the incidence of complications. Two patients developed thrombosis and occlusion of the superior vena cava, which was relieved by the development of a collateral venous circulation. In one patient the broken tip of the lead migrated to a pulmonary artery but did not cause overt complications. The remaining patients were free of symptoms. One patient died for reasons unconnected with pacemaker treatment.

The good toleration of retained pacemaker leads by most patients indicates that major surgical procedures to remove the lead should be reserved for patients with life threatening complications, such as persistent infection or dangerous migration of the lead or both.

Complications of pacemaker treatment such as infection, lead fracture, insulation break, threshold increase (especially with non-programmable pacemakers), and electrode displacement may need corrective surgery to insert a new pacing lead. Removal of primary, now functionless and often defective, leads cannot always be achieved. As a result, there are two or sometimes even more leads in the cardiovascular system, which increases the risk of thrombus formation, infection, or migration of the lead. To assess this risk we studied patients with retained pacing leads.

Patients, methods, and results

The clinical records of permanent pacemaker implantations from January 1972 to January 1982 were reviewed. In 21 patients (17 men, four women; mean age 64.9 (range 51-85) years) implantation of a new pacing lead was necessary in 23 instances because of various forms of malfunction (Table). In all 23 instances the removal of the functionless lead was

Table *Reasons for implantation of a new pacing lead (23 implantations in 21 patients)*

	<i>No of patients</i>
Pacemaker pocket infection	9
Electrode displacement	5
Mechanical penetration	2
Threshold increase	2
Lead fracture	1
Insulation break	1
Unspecified	3

impossible. In 18 instances the lead remained fixed to the right ventricular wall; in five instances it migrated into the right atrium (three cases), the right internal jugular vein (one case), and one of the proximal branches of the right pulmonary artery (one case).

CASE HISTORIES

Case 1—A 63 year old man underwent insertion of the Elema-Schönander EMT 588 lead in January 1972 for complete atrioventricular block. The pacing lead became dislodged on the tenth day after insertion. Repositioning was not achieved, and a new EMT lead was introduced. A third lead was inserted in August 1982 because of extrusion of the box through the skin. Both functionless electrodes remained in the cardiovascular system despite attempts to remove them;

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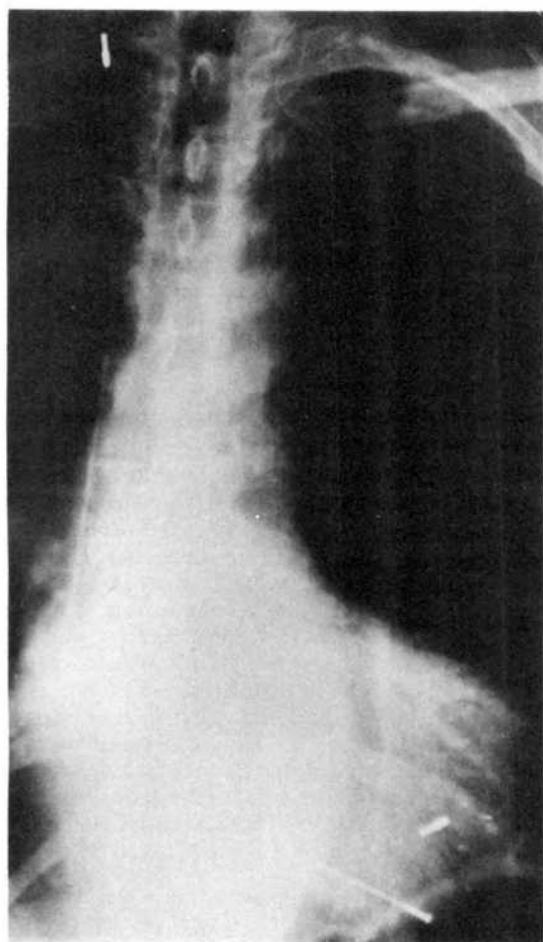


Fig 1 Case 1: chest radiograph showing three pacing leads in the cardiovascular system; one electrode is visible in the right internal jugular vein and two in the right ventricle.

the first lead migrated into the right internal jugular vein (Fig 1).

Case 2—An EMT 588 lead was inserted in August 1972 in a 60 year old man because of complete atrioventricular block. The lead became dislodged two months later; repositioning and removal were impossible, and a second EMT 588 lead was implanted. In May 1983 a third lead was introduced because of late infection of the pacemaker pocket three months after replacement (Fig. 2).

Case 3—A 54 year old man underwent implantation of the LEM lead for intermittent second degree atrioventricular block in March 1976. Pacing ceased in September 1982 because of a threshold increase. During attempted withdrawal the lead broke leaving the tip in the heart. Subsequently, the electrode migrated into one of the proximal branches of the

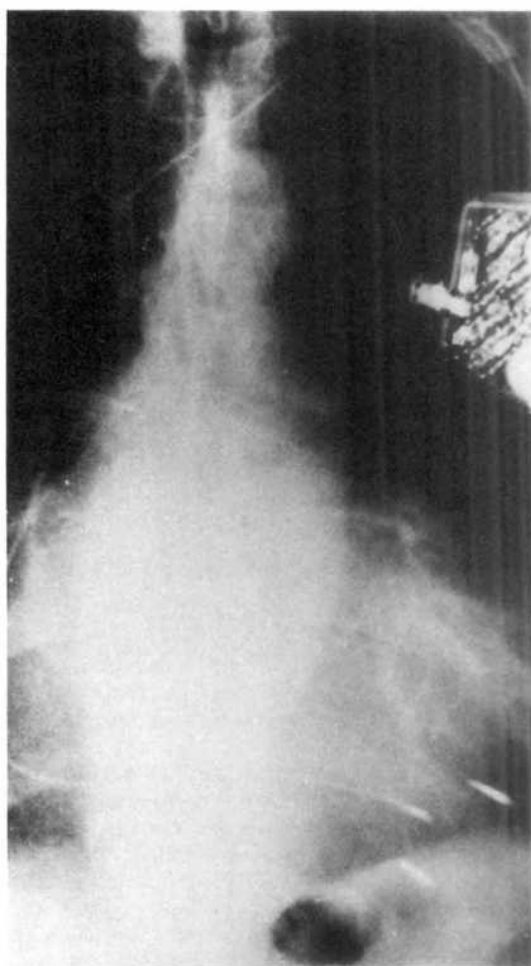


Fig 2 Case 2: chest radiograph showing three pacing leads in the cardiovascular system; the electrodes are visible in the right ventricle.

right pulmonary artery without producing any clinical symptoms and signs either immediately after the event or later during 21 months follow up (Fig. 3).

FOLLOW UP AND OUTCOME

All the patients were followed up to the end of June 1984. The total observation period for patients with two pacing leads was 1097 (range 16–127) months. Mean observation time was 52.2 (median 37) months. Two patients with three leads were followed for 11 and 22 months after the insertion of a third lead.

In two patients, previously reported major venous thrombosis occurred 11 and 24 months after insertion of a new pacing lead.¹ In both cases symptoms and signs of thrombosis and occlusion of the superior vena cava were relieved by the development of collateral

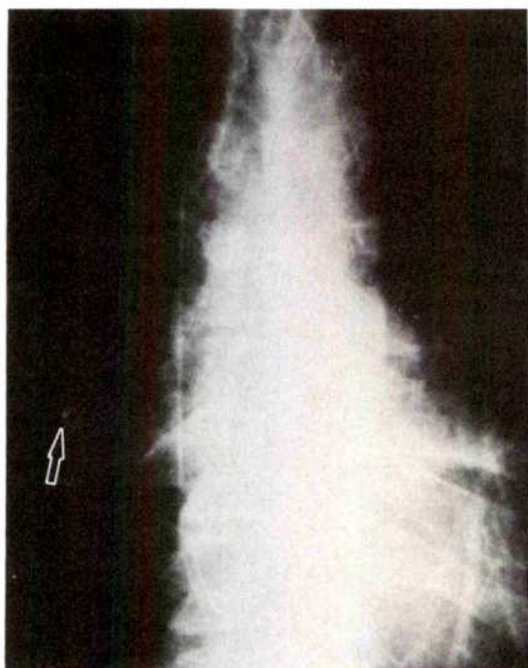


Fig 3 Case 3: chest radiograph showing a migrated electrode (arrow) in the intermediary part of the right pulmonary artery.

venous channels. One patient died 58 months after the insertion of a second lead as a result of gastrointestinal haemorrhage. Two patients were lost to follow up after 16 and 23 months of observation. At the final examination in June 1984 all the remaining patients were free of symptoms and had no signs of thrombosis or infection. Chest x ray films excluded the possibility of serious migration of the pacing leads in all patients.

Discussion

Insertion of a pacemaker lead may predispose to thrombosis or occlusion in axillary, subclavian, or innominate veins, or in the superior vena cava.^{2,3} The venographically confirmed incidence of venous thrombosis in patients with an inserted pacing lead is high and may vary from 28.5%⁴ to 78.5%.⁵ Nevertheless, in most instances the effective circulation is well preserved because of the development of collaterals; thus, the vena cava syndrome or oedema of the arms occurs rarely.⁶⁻⁸

Only one case of overt thrombosis occurred out of a total number of 1201 patients reported by Lagergren *et al.*,⁹ Furman *et al.*,¹⁰ and Kalmar *et al.*¹¹ The incidence of clinically overt venous thrombosis does not seem to be high, in absolute terms, even in patients with two pacing leads. It was not noted in probably the largest reported series of Rettig *et al.*,¹² who fol-

lowed 46 cases for a mean of 21.4 months. On the other hand, as many as half the overall number of thrombotic complications due to pacemaker treatment relate to patients with two pacing leads.¹³ The incidence of subclinical venous thrombosis is also significantly higher in patients with two leads than in those with one.¹⁴ In our experience the successful removal of a functionless lead does not increase the incidence of thrombotic complications. Such a finding has not been reported. Symptoms and signs of venous thrombosis may be encountered as early as 23 days and as late as seven years after the insertion of a pacing lead¹³; more often, they tend to appear after a latent period of approximately 12 months.¹⁵

The possibility of sepsis culminating in endocarditis is a serious risk in patients with retained leads after surgical treatment for infective complications. In Rettig *et al.*'s series there were four deaths due to septic complications, and infection persisted in two cases out of 21 with probably infected leads.¹² There were no infective complications in our series either because the numbers were small or because we adopted the policy of early surgical intervention in case of infection. The risk of fatal infection perhaps justifies attempts to remove infected leads in selected cases by traction.^{11,16,17} Such removal may avoid cardiomy, which may, however, be necessary in cases of life threatening infection.^{12,17} Traction, especially when performed too forcibly, is a hazardous procedure which may cause severe arrhythmias and damage to the heart structures.^{12,17,18} It should therefore be performed under close clinical and electrocardiographic surveillance.

Removal of an implanted pacing lead is often impossible because of the development of a fibrous sheath around the lead which extends along it as far as the superior vena cava.¹⁹ Nevertheless, even when firmly secured a retained lead sometimes frees itself and migrates. The seriousness of this rare complication depends on the size of the portion of the migrated lead and where it became lodged. Migration into the inferior vena cava^{12,20,21} and the pulmonary vascular system^{12,22} has been reported.

A pacing lead in the inferior vena cava was removed by the angiographic snare catheter technique.²⁰ Migration of a portion of lead into the pulmonary vascular bed may be fatal.¹² In contrast, in a patient described by Theiss and Wirtzfeld²² there were no noticeable clinical consequences after migration, which is similar to one of our cases (case 3). Accordingly, in both instances the dislodged fragments were left in situ.

HK died recently.

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Effect of exercise on ventricular response to atrial fibrillation in Wolff-Parkinson-White syndrome

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SUMMARY Ten patients with Wolff-Parkinson-White syndrome underwent cardiac electrophysiological study extended to include the induction of atrial fibrillation at maximum exercise in the upright position. This was performed using a new temporary bipolar lead with a helical active fixation tip for atrial pacing. The highest rate of atrioventricular conduction via the accessory pathway was greater during exercise than at rest in all 10 patients (mean increase 28%). In three cases the resulting ventricular rate exceeded 300 beats/min, but no patient had severe symptoms or ventricular arrhythmias.

The exercise induced enhancement of accessory pathway conduction may significantly but unpredictably affect the risk from spontaneous atrial fibrillation especially in patients with coronary artery disease or in those taking antiarrhythmic drugs. The test procedure was sufficiently simple and well tolerated to be included in our routine electrophysiological investigation.

In patients with Wolff-Parkinson-White syndrome a spontaneous episode of atrial fibrillation may be conducted by the ventricles at a very high rate if the accessory pathway has a short refractory period. This can itself result in syncope and may progress to ventricular fibrillation.¹⁻³ It is in an effort to assess this risk that in the cardiac programmed stimulation study the maximum rate of atrioventricular conduction via the accessory pathway is tested by rapid atrial pacing and induction of atrial fibrillation.

Recently, a young patient underwent such a study, which showed a maximum ventricular rate with atrial pacing, or in atrial fibrillation, of 130 beats/min. A few weeks later, however, he had an apparent syncope attack while playing football. This led us to question whether the standard study, performed with the patient supine and at rest, was able to indicate the full extent of the risk in the ambulant patient.

We therefore extended the electrophysiological investigation to see if upright posture and exercise affected the behaviour of the accessory pathway. We

report here the results of such studies in 10 patients with Wolff-Parkinson-White syndrome who were taking no drugs.

Patients and methods

The 10 subjects were selected from 13 consecutive patients undergoing investigation for Wolff-Parkinson-White syndrome. Two were excluded from this analysis because they were taking antiarrhythmic drugs; one other patient developed disorganised ventricular activity with syncope during the resting programmed stimulation study so that further study during exercise was considered inappropriate. Seven were men, three women; their ages ranged from 14 to 47 (mean 29) years. All patients had electrocardiograms showing consistent delta waves and short PR intervals, and all had regular tachycardias either documented or strongly suggested by symptoms. The delta wave pattern indicated that the accessory pathway was left sided in four, right sided in two, and septal in four.

All patients underwent standard programmed stimulation studies including rapid atrial pacing and the induction of atrial fibrillation at rest. The findings established the potential for orthodromic tachycardia and confirmed that the site of the accessory pathway

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Accepted for publication 29 January 1985

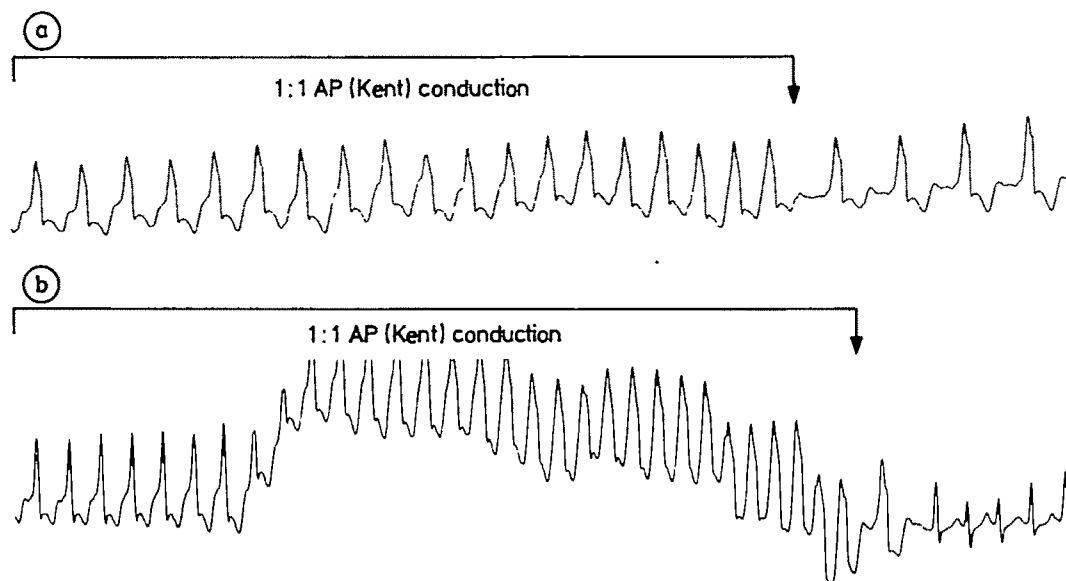


Fig. 1 Electrocardiograms recorded from the same patient during incremental atrial pacing when supine at rest (a) and during peak bicycle exercise in the upright position (b). Loss of atrioventricular conduction via the accessory pathway (AP) (arrowed) occurred at a rate of 240 beats/min at rest and at 330 beats/min during exercise. (In this patient (case 7) the highest rates were achieved during atrial fibrillation.)

had been correctly predicted from the electrocardiogram. No dual accessory pathways were evident.

One of the problems in extending the study to include atrial pacing on exercise is instability of the atrial electrode. We have used a new type of temporary pacing lead with active fixation (OSYPKA TU115S, Siemens-Elema (UK), Sunbury on Thames, Middlesex). It is a No 5 French gauge bipolar lead with a helical tip electrode and a removable stylet, which can be curved for positioning in the right atrium. The lead was inserted via the right subclavian vein in nine patients, in six at the time of the resting stimulating study, and in three as a separate procedure. In one patient with a left sided accessory pathway a standard bipolar electrode in the proximal coronary sinus, inserted via the subclavian vein, was left in place after the resting study and used for the exercise study.

All patients were exercised upright on the bicycle ergometer. The upright position was chosen because previous experience indicated that posture significantly affected the behaviour of re-entry tachycardias including the effective refractory period of the accessory pathway for retrograde conduction.^{4,5}

The bicycle ergometer was used rather than the treadmill because of the better quality electrocardiogram produced and the partial support given to the patient in case faintness developed. The electrocardiogram was monitored continuously as two external

channels and right atrial electrogram. A lightweight portable programmed stimulator (Biotronik USM-30, Biotronik (UK) Ltd, Slough, Berkshire) was also connected to the atrial lead. Resuscitation facilities were immediately available, as were adequate personnel to manage the patient physically and medically should syncope occur.

Exercise was performed with workload increasing by 50 W every 2 minutes up to the maximum capability, in all cases limited by fatigue with sinus rates over 150 beats/min. During peak exercise atrial pacing was started and the rate increased until atrioventricular block occurred and atrial fibrillation was induced as confirmed by the atrial electrogram. Exercise was then stopped, and spontaneous reversion to sinus rhythm occurred in eight cases. One patient reverted to atrial flutter with 2:1 atrioventricular block and one to an orthodromic atrioventricular re-entry tachycardia at 170 beats/min. They were converted to sinus rhythm by atrial pacing using burst overdrive and single timed extrastimulus respectively.

Results

The usual behaviour of atrioventricular conduction in Wolff-Parkinson-White syndrome was seen with incremental atrial pacing at rest: progressive widening of the QRS complexes with increasing pre-excitation. This was due to lengthening delay in the atrioven-

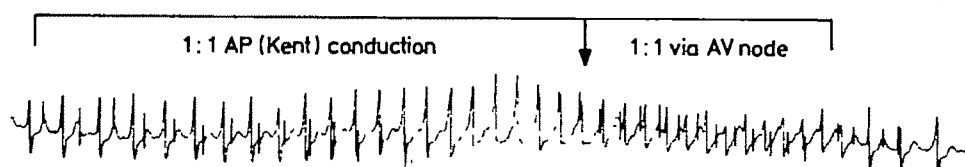


Fig. 2 Electrocardiogram showing the node dominant response to incremental atrial pacing during exercise. In this patient (case 4) the test was performed at submaximal exercise (chosen for illustration); 1:1 atrioventricular conduction was maintained via the atrioventricular (AV) node up to a rate of 320 beats/min after conduction block in the accessory pathway (AP) had developed at 290 beats/min (arrowed).

tricular node as shown by a decreasing HV interval associated with an increasing AH interval. At a rate determined by its refractory period there was sudden block in the accessory pathway resulting in either continued conduction, with delay, by the atrioventricular node and His bundle (which may be called "node dominant" behaviour) or the development of second degree atrioventricular block ("accessory pathway dominant"). Figure 1 shows an example of the latter behaviour, with block occurring at 220 beats/min.

With exercise, as the sinus rate increased, the delta wave became less apparent. This was associated with a shortening of the P to non-delta R wave interval and therefore presumably the atrioventricular nodal conduction time. On atrial pacing the reverse was seen with increasing pre-excitation and widening of the QRS interval at first progressively and then in some cases abruptly probably owing to block in the atrioventricular node, possibly bundle branch block. Atrioventricular conduction continued with little change in the stimulus to R wave interval until in eight patients 2:1 block occurred in the accessory pathway. Figure 1 also shows this accessory pathway dominant pattern with block at a substantially higher

rate (330 beats/min) than at rest in the same patient.

Figure 2 shows the node dominant behaviour seen in the other two patients during peak exercise. There was at first the usual increasing degree of pre-excitation with atrial pacing; the delta wave then suddenly disappeared leaving a narrow QRS complex with a longer PR interval; 1:1 conduction continued, however, to a higher rate at which Wenckebach type block occurred. In these patients the highest rate of accessory pathway conduction was taken as the rate at which the loss of delta wave occurred.

As atrial pacing rate was increased further, atrial fibrillation was induced and conducted irregularly via the accessory pathway or atrioventricular node. In four patients at rest and in three during exercise the shortest interval between two similar pre-excited complexes during atrial fibrillation indicated a higher maximum forward conduction rate via the accessory pathway than seen during the incremental atrial pacing, suggesting that with these cases intra-atrial or pacemaker exit block had been the limiting factor.

The maximum rate of atrioventricular conduction by the accessory pathway was higher during exercise than at rest in all 10 patients. Thus even with this

Table Details of patients and results

Case No	Age (yr)	Sex	AP site*	Resting maximum AP† (beats/min)	Exercise		
					SR‡ (beats/min)	Maximum AP† (beats/min)	% Increase in maximum AP§
1	14	M	Right	130 (N)	150	200 (N)	54
2	30	F	Septal	240	160	300	25
3	31	F	Right	215	185	260	21
4	32	F	Left	260	175	330 (N)	27
5	38	M	Septal	230	175 (AF)	255 (F)	11
6	28	M	Left	230 (F)	175	290 (F)	26
7	16	M	Left	240 (F)	180	350 (F)	46
8	37	M	Left	240 (F)	160	310	31
9	18	M	Septal	270 (F)	170	300	11
10	47	M	Septal	230	160	300	30
Mean	29			229	169	290	28

*AP site, site of accessory pathway.

†Maximum AP, maximum rate of anterograde conduction via the accessory pathway (N, node dominant; F, in atrial fibrillation).

‡SR, sinus rate on exercise just before atrial pacing (AF, atrial flutter with 2:1 block).

§Percentage increase in maximum rate of anterograde conduction via the accessory pathway during upright exercise compared with resting supine.

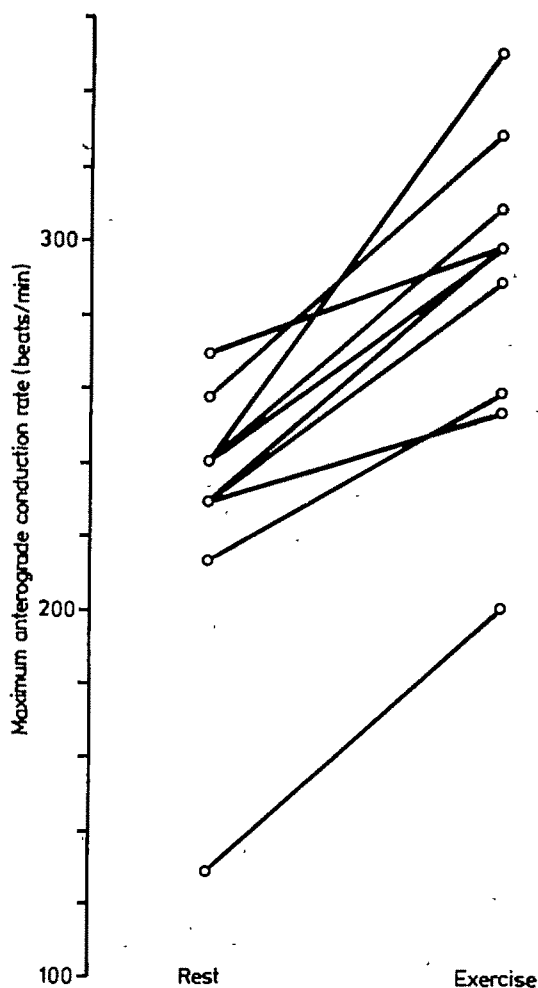


Fig. 3 Individual results from 10 patients showing maximum anterograde conduction rate via the accessory pathway when supine at rest and during peak exercise.

small number the result is statistically highly significant ($p < 0.002$). The Table and Fig. 3 show the individual results; the mean increase was 28%, range 11% to 54%.

In three patients the maximum rate during exercise exceeded 300 beats/min. There was, however, no disorganised ventricular activity, and, although one patient felt moderately faint, all were able to continue pedalling unaided. Most reported that their symptoms were much milder than those produced by incremental atrial pacing during the original resting study.

The procedure resulted in no other complications: in particular, no patients developed symptoms or

signs of myocardial perforation with the use of the active fixation leads.

Discussion

The aims of these studies were twofold: the practical and the scientific. The primary aim was to answer the practical question: is the patient at risk of circulatory collapse or ventricular fibrillation if atrial fibrillation were to occur spontaneously during exercise? The second question was whether exercise had an appreciable effect on the refractory period of the accessory pathway in patients with consistent pre-excitation. Although this has not to our knowledge been tested before, there is some indirect evidence of enhancement of anterograde accessory pathway conduction by exercise.

In a previous study from this laboratory, of tachycardia termination windows, two patients had Wolff-Parkinson-White syndrome and orthodromic tachycardias.⁴ In these, ventricular extrastimuli showed a shorter retrograde refractory period in the accessory pathway with upright posture and exercise resulting in the shrinking or disappearance of the termination window. A result of sustained tachycardia has also been shown by Curry *et al* to be a shortening of accessory pathway refractoriness,⁵ although the mechanism for this probably involves a direct effect of the rate as well as haemodynamic reflexes. Hammill *et al* recently described two patients in whom orthodromic tachycardia could be sustained only in the upright position,⁶ although it was not stated whether block occurred in the normal or the accessory pathway when supine.

There have been several studies in which exercise seemed to facilitate ventricular pre-excitation in sinus rhythm in patients with intermittent pre-excitation.⁷⁻¹⁰ In other similar cases, however, exercise has resulted in block in the accessory pathway^{7 10 11}; this block was probably caused by the increase in sinus rate as shown by both the similar effect of atropine in two^{7 11} and the opposite effect of carotid massage.¹²

An increase in the maximum rate of conduction through the accessory pathway could be expected to be caused by stimulation of adrenoreceptors in the pathway either by circulating catecholamines or by increased tone in the sympathetic innervation. Isoprenaline infusion has been shown to cause recovery of pre-excitation in five patients in whom it had disappeared either spontaneously or after antiarrhythmic treatment.¹² More important to this study are the findings of Wellens *et al*, who measured the effective refractory period of the accessory pathway in seven patients with Wolff-Parkinson-White syndrome and found that in six it shortened after an infusion of iso-

prenaline.¹³ The measurements were made during pacing at a constant rate to avoid any direct rate effect. Cosio *et al* reported a patient presenting with ventricular fibrillation while playing racquet ball, in whom isoprenaline reduced the shortest pre-excited RR interval in atrial fibrillation from 270 to 180 ms.¹⁴

Our results confirm that exercise combined with upright posture significantly increases the maximum rate of atrioventricular conduction via the accessory pathway. The degree of increase, however, varied widely between patients and was not related to age or the site of the pathway.

The haemodynamic tolerance to ventricular rates of up to 350 beats/min during exercise was an unexpected finding. It contrasts with our usual experience that some patients at rest feel severely faint at lower rates, sometimes below 200 beats/min, despite the lower requirement for cardiac output. The difference could be due to catecholamine induced short systole and rapid myocardial relaxation combined with increased venous return from the active leg muscles. The benefits of these mechanisms could be lost should myocardial ischaemia or ventricular failure occur. Thus an important factor in the ability of the study patients to sustain an adequate circulation and continue exercising with high ventricular rates may be the low age of this group and the presumed absence of coronary artery disease. Tolerance of the high rates may also be impaired by drugs which prolong systole or otherwise exert a negative inotropic effect; this could outweigh the intended benefit of prolonging the refractory period of the accessory pathway.

The haemodynamic tolerance may be a major factor determining the risk of ventricular fibrillation. In the context of the first aim of the study the tests were all negative, in that none of the patients had serious symptoms or ventricular arrhythmias in response to the atrial fibrillation. The patient whose collapse prompted the study developed no symptoms during the test but had a vasovagal faint in sinus rhythm after stopping exercise. It should not be concluded from these negative findings that exercise may not in some cases increase the risk from spontaneous atrial fibrillation as the number of patients is low and the proportion of patients with Wolff-Parkinson-White syndrome who have a dangerously short anterograde accessory pathway refractory period is quite small.³

The wide variation between patients in the degree of rate increase was not related to age or the site of the pathway. Moreover, the compensatory haemodynamic responses are determined by several factors that are not readily predictable. Only testing the individual patient can, therefore, determine what additional risk, if any, exercise may entail for that patient. We found that the simple stimulation test during exercise was practicable and rather less

traumatic for the patient than the resting study, allowing us to incorporate it in our routine clinical investigation. Although the prognostic significance of the degree of rate increases with exercise is at present uncertain, the development of syncope or ventricular arrhythmias with this manoeuvre would indicate a need for medical or surgical intervention and a further test to check that the intervention was in fact successful.

It is perhaps paradoxical that patients with electrocardiographic evidence of pre-excitation are generally submitted to programmed stimulation studies only after they have suffered suspected tachycardias. In the case of orthodromic tachycardias our experience suggests that the initiation usually depends on a premature atrial depolarisation conducted anterogradely only via the atrioventricular node followed by retrograde conduction via the accessory pathway: this condition is more likely where the accessory pathway has a longer refractory period. In the case where the presenting tachycardia is atrial fibrillation, the patient's survival has already shown a relatively low risk. It may thus be that patients with pre-excitation and no history of palpitation include some of those most at risk of sudden death.

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Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass *Comparison with disopyramide and digoxin in a randomised trial*

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SUMMARY The efficacy of sotalol in treating acute atrial fibrillation and flutter after open heart surgery was compared with that of a digoxin/disopyramide combination. Forty adult patients with postoperative atrial arrhythmias were randomised into either group 1 (sotalol 1 mg/kg bolus intravenously plus 0.2 mg/kg intravenously over 12 hours) or group 2 (digoxin 0.75 mg intravenously, then two hours later disopyramide 2 mg/kg intravenous bolus and 0.4 mg/kg/h intravenously for 10 hours). In each group, 17 out of 20 patients reverted to sinus or junctional rhythm within 12 hours. The time to reversion in group 1 was significantly shorter than in group 2. Systolic blood pressure fell by ≥ 20 mm Hg or to ≤ 90 mm Hg during drug administration in 17 out of 20 patients in group 1 (sotalol withdrawn in two) and in none out of 20 in group 2. Two patients in group 1 developed transient bradycardia (sotalol withdrawn in one). None of 17 patients in group 1 and two of 17 in group 2 relapsed temporarily into atrial fibrillation during the 12 hours of intravenous treatment. On continued oral treatment, one late relapse occurred in group 1 and five in group 2, and five patients in group 2 had disopyramide withdrawn because of anticholinergic side effects (acute urinary retention in four).

Sotalol was as effective as the digoxin/disopyramide combination and acted significantly faster. Sensitivity to beta blockade in these patients may be related to high plasma catecholamine concentrations known to occur after cardiopulmonary bypass.

Supraventricular arrhythmias (usually atrial fibrillation or flutter) are common in the first few days after open heart surgery, with reported incidences ranging from <20% to >40%.¹⁻³ While a large proportion of these patients eventually return to sinus rhythm, they present an appreciable postoperative management problem. Treatment with digitalis alone is frequently associated with early reversion to sinus rhythm, but an appreciable number of such patients will remain in atrial fibrillation or flutter, often with a persistent rapid ventricular response,⁴ for long periods.

An earlier study in this institution, where the inci-

dence of these arrhythmias is 25%, showed a combination of intravenous digoxin and disopyramide to be significantly more effective than digoxin alone in producing early return to sinus rhythm.⁵ This regimen has subsequently been used in over 200 patients with an overall reversion rate of 60% at 14 hours and 94% at 10 days.⁶ The incidence of serious side effects (19%) prompted us to consider alternative drug treatment.

Sotalol is a non-selective beta adrenergic blocking agent with the additional property of producing pronounced prolongation of the duration of the cardiac action potential (Vaughan Williams class III antiarrhythmic action^{7,8}). The aim of the present study was to compare the efficacy and side effects of sotalol with those of the digoxin/disopyramide combination in adult patients with acute atrial fibrillation or flutter after open heart surgery.

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Accepted for publication 29 January 1985

Patients and methods

All patients undergoing cardiac surgery during the period November 1983 to May 1984 who developed postoperative atrial arrhythmias with a ventricular rate of >120 beats/min were considered for the study. Criteria for exclusion were a history of glaucoma or asthma, severe renal impairment (serum creatinine concentration >0.24 mmol/l), preoperative atrial arrhythmias or atrioventricular block (second or third degree), and the administration of any antiarrhythmic drug (including beta blockers and digitalis) in the previous 48 hours.

If the arrhythmia persisted for at least 15 minutes eligible patients were then randomly assigned, by a sealed envelope system, to either of two groups. The patients in group 1 were given sotalol (Sotacor, Bristol-Myers) 1 mg/kg as an intravenous bolus and then a further 0.2 mg/kg intravenously, given as a continuous infusion in 5% dextrose, over 12 hours. Group 2 received digoxin 0.75 mg intravenously as a bolus. If they reverted to sinus rhythm within two hours they continued to receive digoxin 0.25 mg intravenously twice a day. If not, disopyramide 2 mg/kg intravenously (maximum 150 mg) was then given over 10 minutes followed by an intravenous infusion (in 5% dextrose) at 0.4 mg/kg/h for 10 hours. Written informed consent was obtained from patients allocated to group 1 but not from those in group 2 since they were receiving the standard treatment for such arrhythmias in this institution.

Although the formal comparison between the two treatment regimens ended after 12 hours of intravenous treatment, those patients in group 1 who reverted to sinus rhythm continued to take oral sotalol 160 mg twice daily for the rest of their stay in hospital and for two to three weeks after discharge. Similarly, patients who reverted with digoxin alone continued taking oral digoxin 0.25 mg/day, and those who reverted with the digoxin/disopyramide combination continued taking oral digoxin 0.25 mg/day and disopyramide 150 mg four times a day. The treatment of patients whose arrhythmia persisted at 12 hours was at the discretion of the attending cardiologist and usually consisted of digoxin and either disopyramide or quinidine.

Blood pressure was measured every one to two minutes for 10 minutes, then every 15 minutes for one hour, and then every hour for 12 hours. The electrocardiogram was monitored continuously on a screen, and rhythm strips were recorded at the time of rhythm changes. Twelve lead electrocardiograms were recorded before and 12–24 hours after completion of intravenous treatment. Patients receiving sotalol had blood collected for determining plasma concentrations of the drug at one hour and 12 hours. Assays of plasma disopyramide concentrations were

Table 1 Details of patients

	Group 1	Group 2
No of patients	20	20
Male:female ratio	19:1	15:5
Mean (SD) age (yr)	60.5 (9.1)	63.5 (5.2)
Mean (SD) time to onset of arrhythmia (hr)*	54.4 (16)	55.1 (27.7)
Ratio of atrial fibrillation: atrial flutter	19:1	19:1
Mean (SD) pretreatment systolic pressure (mm Hg)	114 (12)	112 (10)
Mean (SD) pretreatment ventricular rate (beats/min)	163 (24)	158 (17)
No taking beta blockers preoperatively	15	15
No undergoing coronary artery bypass grafting†	17	16
No with preoperative ejection fraction <0.50 ‡	2	2

*Estimated as time from start of cardiopulmonary bypass till onset of index arrhythmias.

†Other operations—Group 1: two patients had coronary artery bypass grafting (CABG), plus carotid endarterectomy and one had ventriculomyotomy for hypertrophic cardiomyopathy; group 2: one had CABG and carotid endarterectomy, one aortic valve replacement, one repair of ruptured papillary muscle, and one repair of ascending aortic aneurysm.

‡At left ventriculography.

not performed in all group 2 patients as the regimen used has been previously shown to produce concentrations in the therapeutic range in similar patients.⁵

STATISTICAL ANALYSIS

Unless otherwise stated, results are given as mean (standard deviation of the mean (SD)). Student's *t* tests were used to test for significance of differences in reversion times and corrected QT intervals (QTc) before and after treatment. The χ^2 test (using Yates's correction factor) was used to test the significance of differences in relapse rates between the two groups.

Results

ANTIARRHYTHMIC EFFICACY

Of 42 eligible patients, 22 were randomised to group 1 and 20 to group 2. One of the group 1 patients refused consent and was given standard treatment (reverted to sinus rhythm after 72 hours), and one reverted spontaneously to sinus rhythm before any sotalol was given. These two patients were excluded from the analysis.

Table 1 shows the clinical details of the remaining 40 patients. Sixteen of the 20 patients in group 1

Table 2 Results

	Group 1	Group 2	<i>p</i> value
Reversion within 12 hr	17	17	NS
Mean (SD) time to reversion (min)	58.8 (68)	187 (164)	<0.01
Relapse within 12 hr	0	2	<0.05
Relapse beyond 12 hr	1	5	

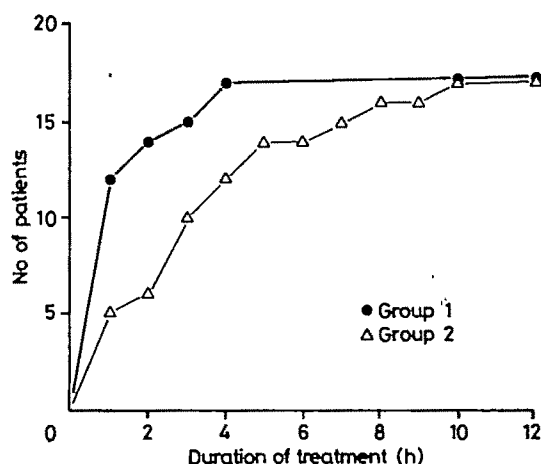


Figure Time course of reversion from atrial fibrillation to sinus rhythm in patients treated with sotalol (group 1, $n=20$) and with a digoxin/disopyramide combination (group 2, $n=20$). One patient in group 1 reverted first to junctional rhythm and then to sinus rhythm (see text).

reverted to sinus rhythm, and one reverted to junctional rhythm (see below) during the 12 hours of intravenous sotalol treatment (Table 2). The times from starting the sotalol bolus infusion to reversion ranged from 5 to 225 (mean 58.8 (67.7)) minutes and included 12 patients who reverted within the first hour (Figure). Plasma concentrations of sotalol were 908 (326) ng/ml at one hour and fell to 372 (154) ng/ml at 12 hours.

Of the three patients who failed to revert, only one received the full dose of sotalol. One patient (who had atrial flutter) was given only 40 mg of a planned 84 mg bolus of sotalol, at which time his systolic blood pressure had fallen from 130 mm Hg to 70 mm Hg, and the drug was withdrawn (see below). He was then given digoxin and disopyramide, and his systolic blood pressure returned to 130 mm Hg over the next two hours. The arrhythmia persisted for the next six days despite continued treatment with digoxin, disopyramide, and, later, quinidine, and he underwent DC cardioversion at that time. A second patient had received 50 mg of a planned 74 mg bolus

of sotalol when his electrocardiographic monitor lead configuration was changed from standard lead I to lead II and ST segment elevation noted. Sotalol was withdrawn, although the ST elevation subsequently proved to be due to postoperative pericarditis. This patient was then given standard treatment and reverted to sinus rhythm during the disopyramide bolus infusion. The third patient remained in atrial fibrillation despite the full 12 hours of sotalol treatment. He returned to sinus rhythm three hours after starting oral digoxin.

In group 2, 17 out of 20 patients reverted to sinus rhythm within 12 hours (Table 2). The times from digoxin bolus to reversion ranged from 5 to 450 (mean 187.7 (164)) minutes and included five patients who returned to sinus rhythm within one hour (Figure). These times were significantly longer than those for group 1 ($p<0.01$). There were six patients who reverted with digoxin alone (at 38.0 (33.7) minutes after the digoxin bolus) and 11 who required the combination of digoxin and disopyramide (reverting 176.6 (200) minutes after disopyramide). The three patients in group 2 whose arrhythmia persisted at 12 hours eventually reverted to sinus rhythm after 19 hours, 20 hours, and 72 hours of continued treatment with digoxin and oral disopyramide.

No patient in group 1 relapsed during the 12 hours of intravenous sotalol, but one who had returned to sinus rhythm four hours after starting sotalol relapsed 19 hours later. Sotalol was continued, and he reverted permanently to sinus rhythm after a further seven hours. A second patient in group 1 relapsed 13 hours after sotalol had been withdrawn, after the development of junctional bradycardia (see below).

Four patients who responded to digoxin alone relapsed 30 minutes to 57 hours later (Table 2). Three were then given disopyramide and one quinidine, and all returned quickly to sinus rhythm. Three patients (out of 11) who responded initially to digoxin plus disopyramide relapsed at 90 minutes, 30 hours, and 32 hours. Two were restored to sinus rhythm soon after a further bolus of intravenous digoxin (0.25 mg), and the third returned to sinus rhythm 30 minutes after starting oral quinidine.

SIDE EFFECTS (TABLE 3)

An appreciable fall in blood pressure was seen during the initial intravenous loading dose of sotalol in 18 out of 20 patients in group 1 (Table 3). In 17 of these, systolic blood pressure fell by at least 20 mm Hg or fell to 90 mm Hg systolic or lower. No patient developed symptoms attributable to hypotension, and in all but two cases (see below) the blood pressure returned towards pretreatment levels over one to two hours despite continued sotalol infusion. Sotalol was withdrawn because of this hypotensive response in

Table 3 Major side effects

	Group 1	Group 2
Hypotension*	17	0
Bradycardia	2	0
Ventricular tachycardia	0	1
Urinary retention	0	4
Drug withdrawn <12 hr	3	0
Drug withdrawn >12 hr	1	6

*Defined as a fall in systolic blood pressure of at least 20 mm Hg or to <90 mm Hg.

two patients. One (who has been mentioned already) had received only 40 mg of a planned 84 mg bolus, by which time his systolic blood pressure had fallen from 130 mm Hg to 70 mm Hg and sotalol was withdrawn. The blood pressure returned to 130 mm Hg over the next two hours. The other patient had sotalol withdrawn after 12 hours, during which his systolic blood pressure, which had been 100 mm Hg before treatment, remained 80–85 mm Hg.

Two patients developed bradycardia during intravenous sotalol administration. One reverted from atrial fibrillation with a very rapid ventricular rate of > 250 beats/min into a junctional bradycardia (50 beats/min) after receiving 50 mg of a projected 90 mg bolus of sotalol. He remained asymptomatic, but sotalol was withdrawn. The junctional rhythm persisted for a further 12 hours, by which time the rate was 90 beats/min. Atrial fibrillation then returned and remained for a further nine hours, during which time 1 mg of intravenous digoxin was given before sinus rhythm was finally restored. Unfortunately, during this second period of atrial fibrillation the patient developed a right hemiparesis of very sudden onset, which proved to be permanent. The second patient reverted to sinus rhythm during the bolus (64 mg) of sotalol but showed several asymptomatic periods of sinus arrest, lasting up to three seconds, over the ensuing 30 minutes. Stable sinus rhythm then returned at a rate of 75 beats/min. Sotalol was not withdrawn, and no further complications were seen.

Sotalol was withdrawn in a fourth patient (who has already been reported) when ST segment elevation, later found to be due to pericarditis, was noted during the bolus injection. No other complications were experienced with sotalol.

There were no appreciable side effects in group 2 patients during the 12 hours of intravenous treatment. There was a statistically significant fall in systolic blood pressure in those 14 patients who received disopyramide (from 113(11) mm Hg to 107(12) mm Hg; $p < 0.05$), but in no case was a fall of > 15 mm Hg recorded. Five patients had disopyramide withdrawn after six to 72 hours of oral treatment because of anticholinergic side effects (acute urinary retention in four, dry mouth in one). One patient who reverted to sinus rhythm 20 hours after starting disopyramide had an episode of sustained ventricular tachycardia requiring electrical cardioversion after a further seven hours of oral disopyramide. This arrhythmia did not resemble torsade de pointes, nor was there abnormal prolongation of the QT interval on the electrocardiogram. Disopyramide was, however, withdrawn, and there was no recurrence of ventricular arrhythmia.

The corrected QT interval (QTc) was prolonged by both disopyramide and sotalol. The value of this interval increased from 0.43(0.05) to 0.47(0.03) ($p <$

0.01) in the 16 group 1 patients who received sotalol for at least 24 hours. Those receiving disopyramide showed a less pronounced increase in QTc from 0.42(0.02) to 0.44(0.04) ($p < 0.01$; $n=15$). The longest QTc interval measured was 0.51 (in a group 1 patient).

Discussion

There are several reasons for supposing that sotalol might be an effective agent for reversion of postoperative atrial tachyarrhythmias. As a non-selective beta blocker it would be expected to have some antiarrhythmic potential and would tend to slow atrioventricular conduction rather than enhance it, a potential danger with disopyramide.⁹ More importantly, sotalol, uniquely among beta blockers, possesses a potent class III antiarrhythmic action⁷ and has shown considerable antiarrhythmic efficacy in several studies.^{10–12}

In this randomised trial, treatment with sotalol proved to be as effective as the digoxin/disopyramide combination in returning patients to sinus rhythm. Furthermore, it acted significantly more quickly and was associated with fewer relapses during the follow up period. The reversion rate of 17 out of 20 (85%) patients after 12 hours of digoxin/disopyramide was higher than the 60% at 14 hours previously observed by us in a much larger group of patients.⁶ The incidence of side effects requiring drug withdrawal (5/20) was similar to our previous experience, although all these events occurred after the 12 hour period of intravenous treatment, as did five of the seven relapses observed. Side effects, particularly hypotension, were, unfortunately, a major drawback with sotalol too, and warrant further discussion.

Sotalol has been given intravenously in similar doses to other groups of patients without reports of such effects on blood pressure.¹⁰ It is known, however, that serum concentrations of adrenaline and noradrenaline rise appreciably at the time of open heart surgery and remain high for two to three days post-operatively.¹³ Furthermore, a recent animal study has shown activation of the sympathoadrenal system, leading to a pronounced increase in plasma catecholamine concentrations during experimentally induced atrial fibrillation.¹⁴ It is possible that these phenomena make such patients peculiarly susceptible to the acute hypotensive effects of beta blockade. Whatever the cause of the hypotension, simply reducing the dosage of sotalol is unlikely to remove the problem, as pronounced falls in blood pressure were routinely observed within two to three minutes of starting the bolus dose (given over 10 minutes). A possible alternative approach would be to give the same loading dose as an infusion over one hour rather

than as a bolus. Given the long plasma half life of sotalol¹⁵ this would be unlikely to lead to appreciably lower plasma drug concentrations at steady state.

Finally, the serum sotalol concentrations obtained were lower than those reported in other studies both of short term intravenous and long term oral administration.^{11,12} They were all within the range regarded as producing beta blockade but generally at the lower end of the range of concentrations found to produce a pronounced class III effect.¹⁶ The first measurement of sotalol concentration was not, however, made until one hour after the administration of the bolus, by which time 12 out of 17 reversions had already occurred. Considerably higher blood concentrations of the drug were probably achieved in the 10 to 20 minutes immediately after the bolus dose.

We thank Mr J Ray for performing the plasma sotalol assays.

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Factors relating to the development of hypertension after cardiopulmonary bypass

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SUMMARY Paroxysmal hypertension after cardiac surgery is a phenomenon of physiological and clinical significance. The possible preoperative and intraoperative factors that may predict its occurrence were studied in 81 consecutive patients undergoing coronary artery surgery (n=58) or valve replacement (n=27), of whom 45 (56%) developed postoperative hypertension. Hypertension occurred significantly more often in those patients who received beta adrenergic blocking agents preoperatively and who underwent coronary artery surgery. Patients with hypertension had significantly higher mean left ventricular ejection fractions preoperatively (52%) than those without (41%) and required phentolamine significantly more often and isoprenaline significantly less often intraoperatively.

It is suggested that the significance of preoperative beta adrenergic blockade, the type of operation, and the intraoperative requirement for phentolamine in patients who developed postoperative hypertension may indicate the role of enhanced sympathetic activity and disturbance of cardiac receptors during surgery. Preoperative myocardial performance and the method of myocardial protection during surgery are likely to influence the occurrence of the hypertensive phenomenon.

Early postoperative hypertension complicating coronary artery surgery is well recognised with a reported incidence of 30-60%.¹⁻³ The hypertensive episode usually develops within an hour of cardiopulmonary bypass, is well established by the time the patient returns to the intensive care unit, and if untreated persists despite adequate analgesia for 6-8 hours. The associated hazards are considerable, including increase in myocardial oxygen consumption, cerebrovascular accidents, and the risk of suture line disruption. Haemodynamic studies show that hypertension after cardiopulmonary bypass is due to increased systemic vascular resistance with practically unaltered cardiac output,^{3,4} and that cardiac reflexes,⁵ the sympathetic nervous system,³ the renin-angiotensin axis,⁶ and vasopressin⁷ may be implicated in this peripheral vasoconstriction. The hypertension responds to vasodilator agents, but a fuller understanding of its cause

may depend on identification of predisposing factors. The purpose of this study was to determine whether certain preoperative and intraoperative factors are predictive of hypertension after cardiopulmonary bypass.

Patients and methods

Eighty one consecutive patients (69 men and 12 women) scheduled for coronary artery surgery or valve replacement were studied prospectively over a three month period in 1983. Of these, 54 patients underwent coronary artery surgery, 23 valve replacement, and four both.

A past history of hypertension was noted, and current medications including beta adrenergic blocking agents and nifedipine were continued preoperatively. These medications were given until 6-10 hours before operation. In 39 patients the left ventricular ejection fraction was determined preoperatively by radionuclide gated acquisition scan.

SURGICAL PROCEDURE

All patients received diazepam (10 mg) two hours

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Accepted for publication 11 March 1984

Table 1 Preoperative clinical characteristics and intraoperative variables in patients with and without hypertension after cardiopulmonary bypass

	Without	With	p value†
Characteristics			
No of patients	36	45	
Mean (SEM) age (yr)	54 (2)	55 (2)	NS
Mean (SEM) ejection fraction (%)	41 (3)	52 (3)	<0.05
No (%) of patients with:			
History of hypertension	8 (22)	12 (27)	NS
Beta blockade treatment	15 (42)	30 (67)	=0.05
Nifedipine treatment	15 (42)	16 (36)	NS
Variables			
Mean (SEM) prime volume (l)	2.0 (0.1)	2.2 (0.1)	NS
Mean (SEM) total bypass time (min)	95 (4)	95 (4)	NS
Mean (SEM) cross clamp time (min)	48 (4)	54 (3)	NS
Mean (SEM) % fall in packed cell volume*	27 (1)	27 (1)	NS
Mean (SEM) no of grafts	2.7 (0.2)	2.5 (0.2)	NS
No (%) of patients given:			
Phentolamine	6 (17)	20 (44)	=0.05
Isoprenaline	21 (58)	9 (20)	=0.05
Metaraminol	4 (11)	4 (9)	NS
Phenylephrine	3 (8)	8 (18)	NS

*Percentage fall in preoperative packed cell volume at onset of cardiopulmonary bypass.

†Fisher's exact test (two tail) or Student's *t* test.

preoperatively with papavaretum (0.3 mg/kg) and scopolamine (0.4 mg) as premedication. Anaesthetic induction was with thiopentone (2–5 mg/kg), papavaretum (0.3 mg/kg), and pancuronium (0.15 mg/kg). Subsequent anaesthesia was maintained with 50% nitrous oxide and oxygen, intravenous boluses of papavaretum and lorazepam, or alphaxalone-alphadolone acetate by infusion. Radial artery and internal jugular catheters were inserted after induction of anaesthesia. During cardiopulmonary bypass metaraminol (0.5–1 mg) or phenylephrine (0.2–1 mg) were given if perfusion pressure was persistently below 50 mm Hg at a pump flow of 2.4 l/min per m². Rises in systemic pressure in the latter phase of bypass were controlled by intravenous boluses of phentolamine (1–5 mg). After bypass isoprenaline was given if systolic pressure fell below 80 mm Hg.

Two surgeons and one perfusionist were involved throughout the study, and pulsatile cardiopulmonary bypass was achieved in all cases with Stockert or Gambro roller pumps and a Bentley SpiraFlo oxygenator. The bypass pump was primed with a measured volume of Hartmann's sodium lactate solution. Moderate systemic hypothermia (27–31°C) was used with intermittent introduction of cold hyperkalaemic cardioplegia solution into the aortic root and topical cold saline into the pericardial sac. Arterial blood gases, electrolyte concentrations, and packed cell volume were measured at hourly intervals. Table 1 gives the preoperative and intraoperative variables recorded for analysis.

POSTOPERATIVE PROCEDURE

On transfer to the intensive care unit all patients were

ventilated to normocarbida. Regular arterial blood sampling and continuous arterial and central venous pressure monitoring were performed. Central venous pressure was maintained with transfusion of blood or plasma at a predetermined level assessed intraoperatively. A bolus dose of papavaretum (10 mg intravenously) was given within 10 minutes of return to the intensive care unit provided that systolic blood pressure was >90 mm Hg. If systolic pressure was persistently >140 mm Hg over the next 10 minutes sodium nitroprusside was infused at an initial rate of 1 µg/kg/min. The infusion rate of nitroprusside was adjusted to maintain systolic pressure at 140 mm Hg. The total dose of nitroprusside given was recorded.

STATISTICAL ANALYSIS

Statistical analysis of data was performed using Fisher's exact test (two tail) or Student's *t* test for unpaired data. Data are expressed either as percentages or as mean values (standard error of the mean).

Results

Of the 81 patients, 45 (56%) fulfilled the criteria for hypotensive treatment according to the study protocol, with mean systolic and diastolic blood pressure at 10 minutes after sedation of 158 (3) and 95 (2) mm Hg. Hypertension was significantly more likely to occur after coronary artery surgery than after valve replacement (37/58 patients vs. 10/27, *p*=0.05) (Table 2).

An analysis of preoperative data showed no significant difference between the postoperatively hypertensive and normotensive patients with regard

Table 2 Characteristics relating to development of hypertension including mean dose requirement of sodium nitroprusside after cardiopulmonary bypass

	Mean (SEM) blood pressure (mm Hg)		Patients with postoperative hypertension		Mean (SEM) ejection fraction (%)	Total dose of sodium nitroprusside (mg/kg)
	Systolic	Diastolic	No	%		
Patients with hypertension	158 (3)	95 (2)				
Patients without hypertension	120 (3)	75 (2)				
Type of surgery:						
Coronary artery bypass graft			37	64*	47 (3)	1.56 (0.32)
Valve replacement			10	37*	44 (6)	2.67 (0.9)
Beta adrenergic blockade:						
Present						1.59 (0.33)
Absent						2.34 (0.64)
Preoperative hypertension:						
Present						2.43 (0.86)
Absent						1.65 (0.3)

* $p = 0.05$.

to age, history of hypertension, or nifedipine treatment (Table 1). Preoperative beta adrenergic blockade, however, was associated with a significantly higher incidence of hypertension after cardiopulmonary bypass ($p=0.05$). The left ventricular ejection fraction, assessed preoperatively in 39 patients by gated acquisition scan, was significantly lower in those who remained normotensive postoperatively ($n=19$) than in the 20 patients who developed hypertension ($p<0.05$). The preoperative ejection fraction did not differ significantly between patients undergoing coronary artery surgery or valve replacement (Table 2).

Hypertensive and non-hypertensive groups were compared for prime volume, total bypass time, cross clamp time, percentage fall in packed cell volume at the onset of cardiopulmonary bypass, and number of coronary arteries grafted. No significant correlation was observed for the development of hypertension with any of these factors (Table 1). The administration of phentolamine during surgery was more common in patients who became hypertensive postoperatively ($p=0.05$), whereas isoprenaline was used more frequently in patients who did not become hypertensive ($p<0.05$). Other intraoperative treatments did not differ between the two groups.

In the hypertensive group the total dose of sodium nitroprusside required to control the hypertensive episode tended to be larger in those patients who had a past history of hypertension, who did not have preoperative beta adrenergic blockade, and in those who had undergone valve surgery (Table 2). These observations, however, did not reach statistical significance.

Discussion

The mechanisms of hypertension after cardiopulmonary bypass have been inconclusively investigated.

Increased systemic vascular resistance with normal cardiac output is characteristic of the haemodynamic profile.^{4,8,9} It is known that certain cardiac reflexes,¹⁰ the sympathoadrenal system, and the renin-angiotensin axis can cause pronounced peripheral vasoconstriction. In some studies of coronary artery surgery, postoperative hypertension has been associated with the severity of coronary artery disease,^{3,8} normality of preoperative angiography,⁸ preoperative beta adrenergic blockade,¹¹ history of hypertension,³ and the number of vein grafts.⁸ The latter two factors were not found to be of importance in this study. An important finding was the lower incidence of hypertension after valve surgery.

Patients who did not become hypertensive postoperatively had a significantly lower ejection fraction preoperatively than hypertensive patients ($p<0.05$). Furthermore, the non-hypertensive patients had a significantly greater requirement for isoprenaline after cardiopulmonary bypass ($p<0.05$). In a study of 28 patients undergoing coronary artery surgery hypertension was reported to occur more often in patients with normal preoperative angiography.⁸ These findings suggest that preoperative myocardial performance is critical to the development of postoperative hypertension, provided that myocardial protection during surgery is adequate. A lower incidence of hypertension in previous reports^{1,3,12} may represent either poorer preoperative myocardial performance or poorer methods of myocardial protection. Moderate systemic hypothermia with intermittent introduction of cold cardioplegia preserves myocardial performance,¹³ affording better protection than either hypothermic ischaemic arrest, intermittent anoxic arrest, or single dose cardioplegia.

The difference in incidence of hypertension according to the type of operation may be related to sympathetic reflexes originating from the heart, great ves-

sels, or coronary arteries. Cardiac reflexes with spinal sympathetic afferent input that are predominantly pressor in nature have been identified.¹⁴ Efferent sympathetic activity producing peripheral vasoconstriction is further observed in the cardiogenic hypertensive chemoreflex¹⁰ in response to stimulation of chemoreceptors in the vicinity of the left coronary artery. Surgical interference with the heart, great vessels, and coronary arteries may stimulate the reflexes, particularly during coronary artery surgery.

In favour of a reflex mechanism for hypertension after cardiopulmonary bypass is the paroxysmal nature of the hypertension and the temporal relation of increasing systemic vascular resistance with cardiac manipulation. Systemic vascular resistance increases in parallel with rises in plasma noradrenaline concentration during bypass⁹ and aortic cross clamping,¹⁵ and both rise to a significantly greater extent in patients who become hypertensive postoperatively.⁸ The major fraction of circulating noradrenaline is derived from innervation of vascular smooth muscle.¹⁶ In our study patients who became hypertensive postoperatively required phentolamine, an alpha adrenergic antagonist, significantly more often during bypass ($p=0.05$), presumably because of increasing systemic vascular resistance. A profound sympathetic stimulus in the heart during bypass is further suggested by the observation that coronary sinus blood contains a higher concentration of noradrenaline than arterial blood immediately after cardiac reperfusion.¹⁵

The sympathetic nervous system may be stimulated by a variety of other influences in the perioperative period including hypothermia,¹⁷ hypotension, alterations in the flow pattern,¹⁸ and haemodilution.¹⁹ Haemodilution may reduce the depth of intravenous anaesthesia on bypass and reduces blood viscosity.¹⁹ Hypertensive and non-hypertensive patients cannot, however, be differentiated on the basis of hypothermia within the small range of operating temperatures in this study. Furthermore, the lack of correlation with total bypass time, volume of prime, and fall in packed cell volume mitigates against the putative contribution of flow changes, hypotension, and haemodilution in influencing systemic vascular resistance.

Patients who received preoperative beta adrenergic blockade were significantly more likely to develop hypertension after cardiopulmonary bypass ($p=0.05$). In the presence of persistent beta adrenergic blockade, adrenergic stimulation may result in unopposed alpha adrenergic activity. The response of peripheral vasodilatation mediated by beta adrenergic receptors is blocked and peripheral vasoconstriction is likely. After withdrawal of propranolol serum and tissue concentrations take at least 48 hours to fall sufficiently to allow a normal response to pharmacological beta

adrenergic stimulation.^{20,21} In a study in which 14 of 15 patients receiving propranolol before coronary artery surgery became hypertensive, a significant correlation was found between postoperative serum propranolol concentrations and dose requirement for sodium nitroprusside.¹¹ In the present study, hypertensive patients who received preoperative beta adrenergic blockade tended to require a higher total dose of nitroprusside, although the difference was not significant.

The renin-angiotensin axis is activated by non-pulsatile renal perfusion,²² but evidence for its activation during cardiopulmonary bypass is conflicting.^{9,23,24} Renin may initiate hypertension through formation of angiotensin II, which is a potent pressor agent, or it may potentiate the vasoconstrictor effect of catecholamines in sustaining hypertension.²⁵ Renin secretion is known to occur in response to sympathetic stimulation, mediated by beta adrenergic receptors.²⁶ Plasma renin activity is depressed during beta adrenergic blockade and remains so for 12 hours after withdrawal of the drug.²⁷ Subsequent values for plasma renin activity show a rebound rise persisting for more than 72 hours in conjunction with a non-significant rise in blood pressure.²⁷ It is not surprising that the role of the renin-angiotensin axis in hypertension after cardiopulmonary bypass hypertension is confused and probably diminished in circumstances of persistent beta adrenergic blockade.

A possible mechanism for hypertension after cardiopulmonary bypass is that of disturbance of cardiac receptors causing increased sympathetic nervous system tone. This is more likely to result in increased systemic vascular resistance in the presence of persistent beta adrenergic blockade. Further study is needed to identify critical surgical influences that trigger cardiac reflexes. An analysis of preoperative data indicates that myocardial performance is contributory to the hypertension. An increased incidence of the hypertensive phenomenon may represent improved myocardial protection during cardiopulmonary bypass.

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Effect of beta₁ selective adrenoceptor blockade on physiological response to exercise

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SUMMARY The effect of the beta₁ selective adrenoceptor blocker, atenolol, on the physiological response to exercise was studied in 12 healthy young men. Oral atenolol (100 mg) and placebo were administered in a randomised double blind crossover fashion an hour and a half before an intermittent multistage cycle ergometer exercise test. At maximal effort oxygen consumption, pulmonary ventilation, carbon dioxide output, and respiratory exchange ratio were not modified by atenolol. In contrast, maximal heart rate and performance time were significantly reduced after atenolol. Nevertheless, because the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate was not changed by atenolol both the absolute and relative oxygen consumption corresponding to 70% and 85% of the maximal heart rate remained unaltered.

These data suggest that recommendations of exercise intensity may be determined on the basis of a calculated percentage of the predetermined maximal heart rate in persons without symptomatic coronary heart disease receiving beta₁ selective adrenoceptor blockers.

Beta adrenoceptor blocking drugs constitute a major advance in cardiovascular therapeutics. Their clinical use in appropriately selected patients with hypertension and angina pectoris is well established.^{1,2} Furthermore, recent data indicate that treatment with beta adrenoceptor blockers can reduce mortality in the early years after myocardial infarction.³ Exercise conditioning has emerged as an important therapeutic factor in the management of these same diseases.^{4,5} Nevertheless, despite the now common practice of prescribing a programme of formal exercise training for patients receiving beta adrenoceptor blockers limited information is available concerning the possible influence of these agents on the currently accepted principles of exercise intensity prescription. In fact, a review of published reports shows only two substantial studies,^{6,7} both of which require further amplification to delineate the precise effect of beta adrenoceptor blockade on the physiological response to exercise. Moreover, although recent research findings suggest an advantage for the use of beta₁

selective adrenoceptor blockers in patients receiving beta adrenoceptor blockade treatment who participate in endurance exercise,^{8,9} the two earlier studies investigated non-selective beta adrenoceptor blockade alone.

To clarify the situation further we examined the effect of the beta₁ selective adrenoceptor blocker, atenolol, on exercise physiology in 12 healthy young men.

Subjects and methods

Twelve healthy, young adult male Caucasians served as subjects. All were volunteers, and informed consent was obtained before the study. The physical characteristics of the subjects included: age 21 (1.2) years (mean (standard deviation)); height 176 (5) cm; body weight 76.26 (6.5) kg; and body fat 14.1 (2.1)%. Each subject gave a clinical history and underwent physical examination, resting and maximal dynamic exercise electrocardiography, pulmonary function tests, serum electrolytes, blood urea nitrogen, and fasting blood glucose measurements, liver function tests, and full blood count, all of which were normal. None of the subjects was taking medication.

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Accepted for publication 29 January 1985

The trial was conducted in a randomised double blind crossover fashion. Each subject received atenolol (tenormin 100 mg) or placebo as a single oral dose an hour and a half before upright exercise performed on a calibrated cycle ergometer (Monark). The selection of a single oral dose was based on the observation that a significant difference was not evident in healthy subjects for submaximal or maximal exercise performance in response to beta adrenoceptor blockers given as a single dose or as twice daily doses for four weeks.¹⁰ Tests were conducted in a controlled environment with a temperature of 20°C dry bulb and relative humidity of 55% and were held at least one week apart.

All subjects were given an initial familiarisation trial. On study days meals, tea, coffee, cola beverages, and cigarettes were avoided for at least three hours before exercise. Before exercise subjects rested for one hour in a comfortable environment. After a four minute warm up at 60 W, the subjects participated in a discontinuous graded exercise test. Subjects started cycling at a work rate of 90 W, the pedal frequency being 60 rpm. The pedal frequency remained constant and the workload was increased by 30 W with each successive three minute exercise period until the pedal frequency could not be maintained. Subjects rested for three minutes between exercise periods. Since initial workload was the same with placebo and atenolol treatment performance time could be measured. Ventilatory variables were measured over the final minute of each work period. Subjects exhaled through a Hans Rudolph valve into meteorological balloons. The expired gas volume was determined in a Warren E Collins chain compensated spirometer, and the oxygen and carbon dioxide contents determined on a portion of the expired gas volume. The gas concentrations were measured with an Applied Electrochemistry S-3A oxygen analyser and a Gould Godart Capnograph Mark II carbon dioxide analyser. Heart rate was calculated from electrocardiograms (CM5 placement) obtained during the final 15 seconds of each workload using a Hellige Multiscriptor EK-33 electrocardiograph, the chart rate being 25 mm/s. Peak heart rate and oxygen consumption attained during exercise were taken as maximal heart rate and

maximal oxygen consumption respectively. Individual and group regression equations relating the percentage of maximal oxygen consumption to the percentage of maximal heart rate were calculated, using standard linear regression analysis, with and without beta adrenoceptor blockade. The percentage of the maximal oxygen consumption and the absolute oxygen consumption were determined from the derived individual regression equations for 70% and 85% of the maximal heart rate with and without atenolol treatment.

The significance of differences between experimental variables was analysed using a paired *t* test. Statistical significance was established at the 0.05 confidence level.

Results

Table 1 shows the effect of atenolol on cardiorespiratory variables at maximal exercise and exercise performance. Maximal oxygen consumption, pulmonary ventilation, carbon dioxide output, and respiratory exchange ratio were not significantly altered by beta adrenoceptor blockade. Maximal heart rate was, however, reduced by 23.1% ($p < 0.001$) and cycle ergometer performance time by 4.2% ($p < 0.05$) after treatment with atenolol.

Despite the considerable negative chronotropic effect of atenolol during exercise, the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate was not modified (Figure) during beta adrenoceptor blockade in the present study. Likewise, both the relative and absolute oxygen consumptions for 70% and 85% of the maximal heart rate were unaltered by atenolol (Table 2).

Discussion

Whereas some researchers have reported a decrease in maximal oxygen consumption after beta adrenoceptor blockade,¹¹⁻¹³ others have not found such an effect.¹⁴⁻¹⁶ Recently, Tesch and Kaiser attributed this inconsistency to differences in test subject selection, and their findings with the non-selective beta adrenoceptor blocker propranolol indicated that a

Table 1 Effect of atenolol during maximal exercise on cardiorespiratory variables and exercise performance. Figures are mean (SD) values ($n=12$)

	Placebo	Atenolol	% Change
Maximal oxygen consumption (l/min)	3.43 (0.37)	3.36 (0.36)	2
Pulmonary ventilation (l/min)	104.0 (12.9)	103.7 (12.9)	0.3
Carbon dioxide production (l/min)	3.87 (0.48)	3.85 (0.49)	0.5
Respiratory exchange ratio	1.14 (0.04)	1.15 (0.05)	0.9
Heart rate (beats/min)	199 (7)	153 (11)	23.1*
Performance time (min)	20.25 (3.07)	19.4 (2.41)	4.2†

* $p < 0.001$; † $p < 0.05$

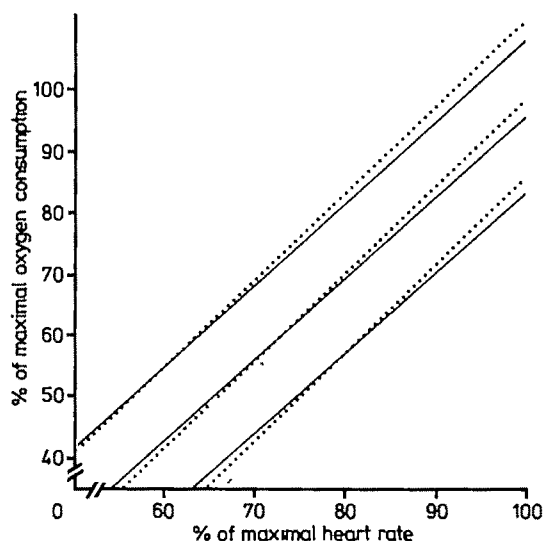


Figure Effect of atenolol on the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate in 12 healthy subjects. Regression lines together with 95% confidence limits are shown for placebo (solid lines) and atenolol (broken lines). The equations for the regression lines are: placebo— $y = 1.32x - 36$ ($r = 0.95$); atenolol— $y = 1.40x - 42$ ($r = 0.95$), where y is the percentage of maximal oxygen consumption and x the percentage of maximal heart rate.

significant reduction in maximal oxygen consumption could be expected in physically active men after pharmacological blockade of beta adrenoceptors.¹¹ In the present study, however, maximal oxygen consumption was essentially unaltered by atenolol. We suggest that this seemingly conflicting observation can be ascribed to differences between beta₁ selective and non-selective beta adrenoceptor blockade⁹ and to our use of an intermittent test protocol. Regarding the latter, the fatiguing effect of beta adrenoceptor blockade^{8,9} might prevent subjects from attaining their true maximal oxygen consumption during exercise testing, a response which is likely to be lessened by the use of an intermittent as opposed to continuous test protocol.

At present it is widely accepted that endurance conditioning performed at 70% to 85% of the predetermined maximal heart rate will yield the exercise intensity needed for the stimulation of a physiological training effect.^{6,17,18} Our study shows that, although the reduction in maximal heart rate is considerable during beta adrenoceptor blockade, atenolol does not alter the relation of percentage of maximal oxygen consumption to percentage of maximal heart rate in healthy subjects. Furthermore, because the maximal oxygen consumption was not reduced by atenolol in our study the absolute as well as the relative oxygen consumption corresponding to 70% and 85% of the maximal heart rate were not significantly modified. Thus, although our finding cannot be extrapolated to patients with coronary heart disease whose exercise is limited by angina pectoris, the present data suggest that exercise intensity may be determined by using a calculated percentage of the predetermined maximal heart rate and should yield the expected relative and absolute exercise intensity in physically active patients with hypertension or asymptomatic coronary heart disease treated with beta₁ selective adrenoceptor blockers. In addition, since beta adrenoceptor blockade appears to exert its greatest effect on the cardiorespiratory response to exercise in young physically active subjects¹¹ the present finding is also likely to be applicable to older less active patients.

Previously, Hossack *et al* and Pollock and Foster investigated the effect of propranolol on exercise training programmes in subjects with⁶ and without⁷ coronary heart disease respectively. Both groups reached a similar conclusion to that of the present study regarding relative exercise intensity prescription, but no data were presented for the absolute oxygen consumption corresponding to a specific heart rate range. Although a note of caution is appropriate concerning a further interpretation of their findings, it does appear on analysis of their results^{6,7,19} that during propranolol treatment the absolute exercise intensity for a given percentage of the maximal heart rate is, in contrast to our findings with atenolol in healthy subjects, essentially unchanged or increased in

Table 2 Effect of atenolol on absolute and relative oxygen consumption for 70% and 85% maximal heart rate. Figures are mean (SD) values ($n = 12$)

	Placebo	Atenolol	% Change
70% maximal heart rate:			
Heart rate (beats/min)	139 (5)	107 (8)	23*
Oxygen consumption (l/min)	1.86 (0.35)	1.79 (0.38)	3.8
% maximal oxygen consumption	53.9 (6.5)	53.0 (7.5)	1.7
85% maximal heart rate:			
Heart rate (beats/min)	169 (6)	130 (10)	23.1*
Oxygen consumption (l/min)	2.59 (0.36)	2.59 (0.39)	0
% maximal oxygen consumption	75.3 (4.5)	77.0 (5)	2.3

* $p < 0.001$.

patients with coronary heart disease (depending on the precise cardiac status) and decreased in healthy subjects. This observation may be of clinical as well as scientific importance. The interaction of exercise conditioning and beta adrenoceptor blockade is presently controversial in that patients with coronary heart disease seem capable of deriving a pronounced training effect,²⁰⁻²² whereas the training effect appears to be significantly attenuated with non-selective but not beta₁ selective beta adrenoceptor blockade in healthy subjects.²³ While it is commonly believed that the magnitude of the physiological adaptation to exercise training is dependent on the relative rather than the absolute exercise intensity,¹⁷ this might not be entirely true for a given subject with and without beta adrenoceptor blockade. We speculate that the different training responses in subjects receiving beta₁ selective and non-selective beta adrenoceptor blockers and with a different cardiac status might be partly related to the differing effect of these variables on the absolute exercise intensity corresponding to a specific percentage of the maximal heart rate.

This study was supported by grants from ICI (South Africa) and Execucare Preventive Fitness Maintenance.

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Valve prolapse in Behçet's disease

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SUMMARY Valve prolapse was diagnosed solely by echocardiography in three consecutive patients with Behçet's disease. Two patients had prolapse of the posterior mitral valve leaflet, but no clinical manifestations of valve prolapse. In the third patient aortic valve prolapse was associated with physical signs of aortic regurgitation and left ventricular failure.

Valve prolapse in these cases may have resulted from structural and functional derangement caused by the underlying non-specific vasculitis that occurs in Behçet's disease.

Behçet's disease (or syndrome) is now recognised to be an autoimmune disorder showing evidence of multisystem involvement and widespread vasculitis as its basic pathohistological features.¹⁻⁴ Associated cardiovascular lesions have been well documented in recent years and have actually been considered as the major cause leading to fatal outcome.^{5,6} Prolapse of cardiac valves is one of the complications not previously described. This report presents the brief histories, related clinical data, and echocardiographic features indicating mitral or aortic prolapse in three consecutive cases and suggests the frequent development of such pathological changes in the course of Behçet's disease.

Patients and methods

CASE REPORTS

Case 1—A 36 year old woman presented to our clinic in 1975 suffering from an intermittent low grade fever associated with oral and genital ulcers, conjunctivitis, erythema nodosum on both legs, and arthralgia. Physical examination of the cardiovascular system was normal. The erythrocyte sedimentation rate was 34 mm in the first hour. The electrocardiogram showed frequent ventricular extrasystoles. She was treated with oral steroids with good symptomatic relief. In December 1979 segmental colitis was diagnosed at laparotomy. The cardiovascular manifestations appeared in April 1982 when she had attacks of palpitation and pronounced dyspnoea, and typical

echocardiographic signs of mitral posterior leaflet prolapse were found. Hypertension was diagnosed in February 1983.

Case 2—A 63 year old woman was admitted in August 1978 with a history of fever (up to 39°C) a month before and painful orogenital ulcers three days after the onset of fever. Physical examination showed severe anaemia, bilateral conjunctival hyperaemia, small ulcers on the buccal mucosa and tip of the tongue, and dark red nodules on both legs. Her erythrocyte sedimentation rate was 120 mm in the first hour. A skin biopsy specimen from the left forearm showed thickening and mild inflammatory cell infiltration of the wall of some small veins. After admission her symptoms were controlled with antipyretic and antibiotic drugs. She was discharged in September 1978. Follow up examinations in 1983 detected no abnormal findings, but a cross sectional echocardiogram showed typical signs of mitral valve prolapse (Figure).

Case 3—A 58 year old man was seen in 1969 with low grade fever, ulcers in the mouth, chronic conjunctivitis, and erythema nodosum on the dorsum of the feet. In August 1982 he began to experience frequent attacks of precordial tightness without any obvious precipitating causes. The electrocardiogram showed left anterior fascicular block and left ventricular hypertrophy. He was admitted in January 1984 with shortness of breath and orthopnoea, mild oedema of both legs, and multiple small ulcers on the buccal mucosa, tongue, and external genitalia. His blood pressure was 140/80 mm Hg and the cardiac rhythm regular. There was a blowing diastolic murmur of moderate intensity at the left sternal border (second and third intercostal spaces). The erythrocyte sedimentation rate was 54 mm in the first hour. Immune complexes were present in the blood, and he

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Accepted for publication 15 February 1985

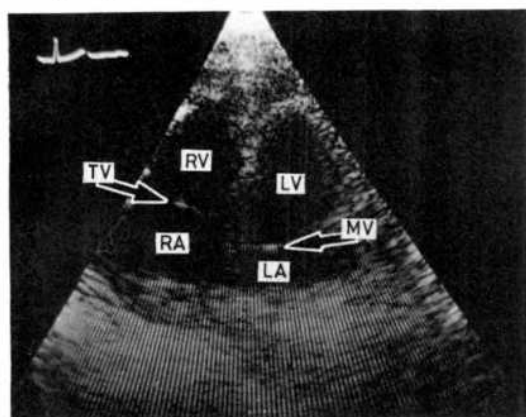


Figure Case 2: Cross sectional echocardiogram in the apical view of four cardiac chambers showing the mitral valve (MV) bulging beyond the atrioventricular annulus into the left atrium (LA) during mid and late systole. RV, right ventricle; LV, left ventricle; RA, right atrium; TV, tricuspid valve.

had raised concentrations of serum IgA and IgG. The cross sectional echocardiogram showed prolapse of the right coronary cusp of the aortic valve and associated aortic incompetence. After admission, oral steroids, cardiotonics, and diuretics were given to improve cardiac function, but cardiac insufficiency and pulmonary congestion were refractory to these measures. Oral ulceration could be controlled only with cyclophosphamide.

ECHOCARDIOGRAPHIC FINDINGS

In cases 1 and 2 the mid and late systolic hammocking of the mitral valve was shown on the M mode echocardiogram and in the cross sectional apical four chamber view (Figure). The mitral leaflets bulged beyond the atrioventricular valve annulus into the left atrium during systole. In case 3 prolapse of the aortic valve cusp during diastole was shown on the cross sectional image of the heart in the long parasternal axis view.

Discussion

The clinical features of all three cases fulfil the diagnostic criteria of the complete type of Behçet's disease. The cardiovascular manifestations in Behçet's disease have attracted attention in recent years. The incidence as reported by James was around 30%, and the vascular lesions appeared to be the major cause of death in those with such complications.^{3,5,6} Valve prolapse occurred in three consecutive patients, who make up 50% of our total series of six patients with Behçet's disease. This frequent association of the two conditions in the absence of other obvious aetiological factors suggests that a causal relation may exist.

Recently, it has been suggested that mitral valve prolapse may be an autoimmune disease.⁷ It occurs in collagen vascular diseases such as polyarteritis nodosa, scleroderma, and systemic lupus erythematosus and in disorders of collagen formation such as Marfan's syndrome.^{8,9} We consider that the valve prolapse in the present three cases may have been the result of structural damage and functional derangement caused by the underlying non-specific vasculitis of Behçet's disease, but histological examination would be necessary to confirm or refute such a hypothesis.

The aortic regurgitation detected in case 3 caused cardiovascular deterioration, and hence such prolapsing valve lesions may have important prognostic consequences. The situation was less serious in the two patients with mitral valve prolapse. In both there were no physical signs of prolapse, and the diagnosis was made purely on echocardiographic grounds. Such an absence of physical signs is common in patients with mitral valve prolapse due to any cause. The clinical significance of echocardiographically documented prolapse in Behçet's disease is at present unknown, but follow up will establish whether such patients develop overt mitral regurgitation or the other complications of mitral valve prolapse such as arrhythmias, emboli, and bacterial endocarditis. In the meantime it seems sensible, in a multisystem disorder like Behçet's disease, to document the presence or absence of cardiac valve prolapse by routine echocardiographic screening.

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Case reports

Diffuse non-specific aortitis with multiple saccular aneurysms and aorto-enteric fistula

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SUMMARY A rare variant of non-specific aortitis was found at necropsy in a young hypertensive woman. The aorta showed severe, extensive, non-specific aortitis with multiple saccular aneurysms containing thrombi throughout its length except for 2 cm from its bifurcation. A fistulous tract was identified leading from an aortic aneurysm at the level of the renal arteries to the second part of the duodenum. Both renal artery ostia were narrowed. The small intestine contained 2 litres of blood, at necropsy. Bilateral ischaemic atrophy of the kidneys was present.

Non-specific aortitis is not ubiquitous in distribution. This disease was first described as an entity from Japan.¹ Non-specific aortitis with multiple saccular aneurysms has been reported only from South Africa.²⁻⁴ None of the cases in these series had developed spontaneous aortic fistula. We report a case of severe, extensive non-specific aortitis with multiple saccular aneurysms and spontaneous aortoduodenal fistula.

Case report

CLINICAL HISTORY

A 22 year old woman was found to be hypertensive during a routine check up. Three years later she noticed a lump in the abdomen and since then had suffered from severe intermittent back pain.

On examination all peripheral pulses were felt, there was no brachiofemoral delay, and blood pressure ranged between 170-200/130-140 mm Hg. Prominent suprasternal pulsations, left ventricular heave, loud and split second heart sound with prominent aortic component, and a fourth heart sound were noted. A pulsatile mass measuring 5 cm×5 cm was present in the epigastrium. Grade two retinopathy was also present.

Her haemoglobin concentration was 11 g/dl, erythrocyte sedimentation rate 54 mm in the first hour, and blood urea concentration 6.7-8.3 mmol/l (40-50 mg/100 ml). Chest radiographs showed a normal size

heart, widened aortic arch, and prominent descending thoracic aorta. An electrocardiogram showed sinus rhythm with left ventricular hypertrophy. On the day scheduled for aortography she developed profuse haematemesis and died from circulatory shock.

NECROPSY FINDINGS

Only a 15 cm midline abdominal incision was permitted. The heart weighed 420 g and showed left ven-

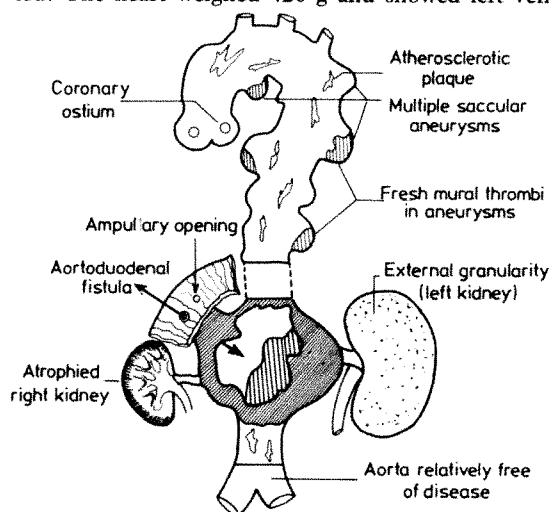


Fig. 1 Diagram showing the aorta, multiple aneurysms, aortoduodenal fistula (bidirectional arrow), and atrophied right kidney with severely stenotic left renal artery. Thrombi are seen within the aneurysms. Atherosclerotic patches are also present.

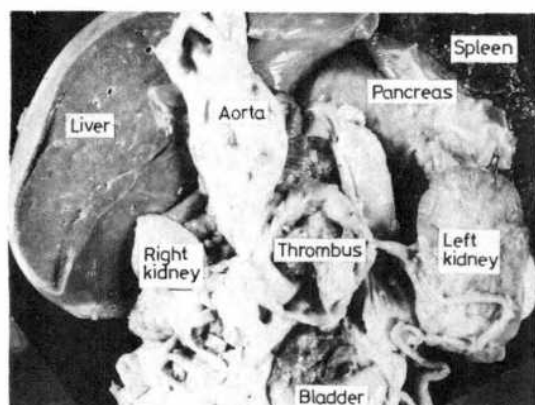


Fig. 2 Morphological appearance of the abdominal aorta, an aneurysm at the level of renal vessels with thrombus, severely atrophied right kidney, and granular left kidney. The liver, spleen, pancreas, and urinary bladder are also shown.

tricular hypertrophy and dilatation. The proximal 2 cm of the left main coronary artery showed fatty streaks.

The aorta was dilated and irregularly tortuous in its entire length and showed multiple saccular aneurysms varying from $1 \times 0.5 \times 0.3$ cm to $7 \times 6 \times 4.5$ cm in size (Fig. 1). The thickness of the wall of the aorta varied from 0.1 cm to 0.3 cm. The intimal surface was pink and was of the consistency of puff pastry throughout, except for the terminal 2 cm near its bifurcation. In addition, there were interspersed atherosclerotic plaques and ulcers in the intima. Most of the aneurysms were filled with fresh as well as partially organised thrombi. The largest one, situated at the level of the renal vessels (measuring $7 \times 6 \times 4.5$ cm) was partially filled with an organised thrombus. A probe could be passed from its floor through a tunnel (0.9 cm in diameter) to the second part of the duodenum situated 2.6 cm distal to the opening of the bile duct. The right renal artery ostium was narrowed, thickened, and roughened and that of the left artery occluded by an organised thrombus. The main branches of the aorta, except the renal arteries, were free of disease.

Multiple sections from the diseased atherosclerotic and relatively normal looking aorta and also from the wall of the aneurysms were stained with haematoxylin and eosin, Masson's trichrome stain, and phosphotungstic acid haematoxylin and examined. The aorta showed features of non-specific aortitis with pronounced thickening of the intima due to increased fibrocollagenous tissue, smooth muscle proliferation and deposition of basophilic intercellular substance. The media showed variable destruction of muscle and elastic tissue with replacement fibrosis. The outer two thirds of the media showed prominent neovascularisation.

The outer media along with the adventitia, which was of variable thickness, showed inflammatory cell infiltration consisting of lymphocytes, histiocytes, and plasma cells. These were mainly perivascular in distribution. Occasional epithelioid cell granulomas were identified. Endarteritis obliterans or fibrinoid necrosis was conspicuously absent.

The aneurysmal wall showed almost total destruction of elastic tissue, pronounced replacement fibrosis of the media, and thickening of the adventitia. Fresh thrombi were identified on the mural surface.

The right and left kidneys weighed 20 g and 120 g respectively. The external surface showed fine and coarse granularity (Figs. 1 and 2). Microscopical examination showed features of ischaemia and benign nephrosclerosis. The pelvicalyceal system and ureters were normal.

Discussion

Non-specific aortitis with multiple saccular aneurysms has been reported from Africa.²⁻⁴ This type is uncommon in India, and to the best of our knowledge such a case has not been documented at necropsy. A few cases of non-specific aortitis with multiple aneurysm formation, however, have been reported in a contrast study (S Bhargava, personal communication). The South African variety of aortitis is diffuse and the aneurysms are characteristically multiple and saccular compared with the other varieties of aortic aneurysms reported in various series,^{5,6} in which they are fusiform and not multiple.

An aortoenteric fistula was found in the present case. This is unusual in non-specific aortitis. On the other hand fistulous tracts are not uncommon in the fusiform abdominal aneurysms described in various series, and about 31% cases rupture into the duodenum.⁷⁻¹⁰ Although multiple saccular aneurysms have been reported in cases of aortitis seen in South Africa, in none of these cases has an aortoenteric fistula been reported.

The aetiology of the multiple aneurysms in this case was determined by exclusion. Syphilitic origin was unlikely since aneurysms in this disease are most commonly found in the ascending aorta, although the abdominal aorta is the affected site in about 10% of cases. Multiple aneurysms are unusual in syphilis. Multiple aneurysms may also result from severe and extensive atherosclerosis, which is an unlikely cause in this case for several reasons. Firstly, this patient was a young woman. Secondly, at necropsy the process of atherosclerosis was only patchy, and thirdly, in the non-atherosclerotic areas of the aorta also there was pronounced thickening of all the layers—namely, the intima, media, and adventitia. It thus appears from the histological features that in this case the mul-

tiple aneurysms resulted from a severe, diffuse, non-specific aortitis.

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Persistent left sided fifth aortic arch in a neonate

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SUMMARY A persistent left sided fifth aortic arch with coarctation of the aorta and persistence of the ductus arteriosus was recognised and treated surgically in a newborn infant. The fifth arch was used to repair the coarctation, and five years later the child had normal peripheral pulses and no residual murmurs.

Persistence of the fifth aortic arch is a rare congenital defect. It has been left sided and associated with tricuspid atresia and cor triatriatum,^{1,2} coarctation of the aorta,³ persistence of the ductus arteriosus,^{4,5} and with pulmonary atresia and ventricular septal defect.^{6,7} Necropsy findings have been reported in four of these cases.

Case report

A male infant (birth weight 3 kg) born after a full term pregnancy and normal delivery showed respiratory distress and slight cyanosis 24 hours later. The liver was palpable 3 cm below the right costal margin. Both axillary and femoral pulses were weak. A mid systolic murmur was audible over the upper left sternal edge, the second heart sound was loud in the pulmonary area, and gallop rhythm was present at the cardiac apex. An electrocardiogram showed right atrial enlargement and right ventricular hypertrophy. Chest radiographs indicated pulmonary oedema and moderate cardiomegaly with left atrial enlargement. Cardiac catheterisation 48 hours after birth showed systemic pressures and high oxygen saturations in the pulmonary artery due to persistence of the ductus arteriosus. The mean left atrial pressure was 20 mm Hg. The injection of contrast medium into the left ventricle showed in the lateral view (Fig. 1a) two aortic arches with the brachiocephalic trunk, the left carotid and the left subclavian arteries arising from the upper arch. The lower arch, which was of similar size, arose from the aorta at the level of the brachiocephalic trunk and joined the upper arch above an area of coarctation below which the ductus arteriosus arose. It was concluded that this lower arch was a persistent

fifth aortic arch. The frontal view (Fig. 1b) showed a left sided aortic arch and the brachiocephalic trunk as its first branch.

Surgical treatment was performed immediately; the ductus was ligated and the fifth aortic arch was separated from the ascending aorta and used to reconstruct the fourth arch by making an anastomosis of 0.8 cm diameter between proximal and distal portions of the normal aorta (Fig. 2a and b). Five years later axillary and femoral pulses were normal and no murmurs were audible.

Discussion

Embryological evidence of a fifth aortic arch became accepted in man in 1922.⁸ Forty seven years later the necropsy finding of a fifth aortic arch complicated by tricuspid atresia and a divided left atrium was reported.¹ Anatomically, the fifth aortic arch emerges from the aorta at the proximal portion of the fourth arch and ends in the distal portion of the sixth.

Persistence of a fifth aortic arch has to be differentiated from a retro-oesophageal right subclavian artery and from a double aortic arch. Both can be distinguished by angiography; in the former the frontal view shows the right subclavian and right carotid arteries arising separately from the aorta; in the latter, the lateral view shows superimposition of the double arches in contrast to the separate but parallel positions of the fourth and persistent fifth aortic arches. The differentiations can be confirmed by radiological examination with a barium filled oesophagus, which is compressed laterally or posteriorly by either an anomalous right subclavian artery or by part of a double aortic arch. Further confirmation can be obtained by cross sectional echocardiography.

Persistence of the fifth aortic arch is a different anomaly when associated with pulmonary atresia. It

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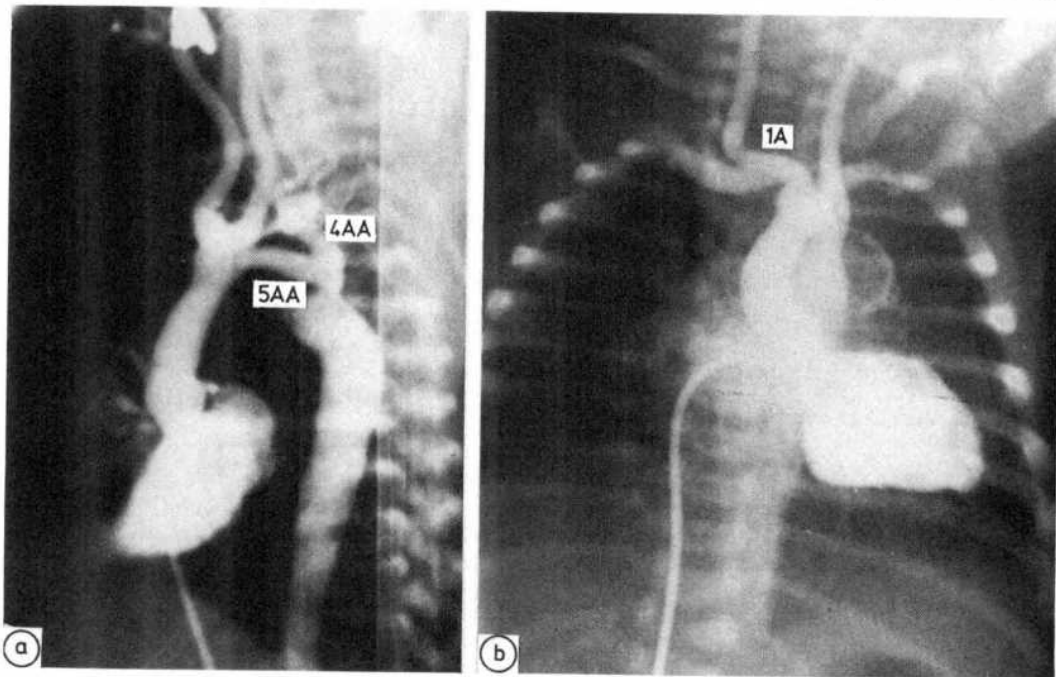


Fig. 1 Angiocardiograms in (a) the lateral and (b) the posteroanterior view after injections of the left ventricle. (a) Two images can be seen, the upper one (4AA) emerging from the supra-aortic trunk, the lower one corresponding to the fifth aortic arch (5AA). Coarctation of the aorta and initial filling of the ductus arteriosus are also seen. (b) The brachiocephalic trunk is well developed and is seen as the first vessel (1A) emerging from the aorta. 4AA, fourth aortic arch

can then be a naturally occurring source of pulmonary arterial supply,^{6,7} is not comparable with the present case report, and would not have been available for incorporation in the surgical repair.

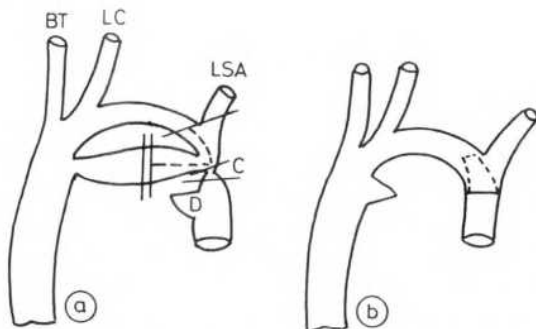


Fig. 2 Diagram showing the position of the fourth (4AA) and fifth (5AA) aortic arches, the persistent ductus (D) and the coarctation (C) before (a) and after (b) surgical repair. BT, brachiocephalic trunk; LC, left carotid (artery); LSA, left subclavian artery.

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Transient Q waves followed by left anterior fascicular block during exercise

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SUMMARY A 45 year old white man developed transient abnormal Q waves and ST segment elevation preceding left anterior fascicular block during exercise stress testing. The simultaneous disappearance of Q waves and fascicular block suggested that the abnormal Q waves were determined by an early septal conduction defect.

Transient abnormal Q waves have been described during selective cardiac surgery, hyperkalaemia, shock, severe metabolic stress, and acute coronary insufficiency.¹ Isolated reports exist about Q waves occurring during stress testing.² We report a patient with two vessel coronary artery disease in whom exercise stress testing induced transient abnormal Q waves, ST segment elevation, and left anterior fascicular block.

Case report

A 45 year old white man was admitted to our ergometric laboratory for evaluation because of recurrent chest pain. For two years he had had infrequent episodes of a retrosternal burning sensation that radiated to the left arm and lasted for 10 to 15 minutes. He smoked 30 cigarettes a day.

On examination the resting heart rate was 67 beats/min and the resting blood pressure 120/80 mm Hg. The resting electrocardiogram showed (Fig. 1) sinus rhythm, QRS axis, +70°; QRS width, 80 ms; and RS pattern from V1 to V3 with T wave inverted in V1 and diphasic in V2.

Bicycle stress testing was performed with a workload that was increased by 30 W at three minute intervals. After five minutes of exercise (60 W), at a heart rate of 130 beats/min and blood pressure of 185/105 mm Hg, he developed progressive chest pain; at that time a QS pattern appeared in V1-V2 and the R voltage was reduced in V3 simultaneously with ST segment elevation from V1 to V4. The QRS axis shifted to +30°, and the QRS width increased to 90 ms. The

exercise test was stopped. At the fourth minute of the recovery period at a heart rate of 82 beats/min a further ST segment elevation in V2-V5, an increase in QRS width to 110 ms, and a shifting of QRS axis to -40° were noted. After 10 minutes rest at a heart rate of 70 beats/min the R waves in V1-V2 reappeared and the QRS axis and width returned to the pre-exercise values. Cardiac enzyme activities immediately and at three and six hours after exercise testing were normal (creatinine phosphokinase = 75 U/l, 85 U/l, and 72 U/l, respectively). Cross sectional echocardiography, performed in the supine position and the left lateral decubitus using the apical approach at the time of interruption of the exercise testing, did not show any segmental wall motion abnormality at qualitative real time inspection. At the sixth minute of the recovery period, when the QRS axis was at -40°, apical echocardiography was repeated and did not show any modification (Fig. 2).

Coronary angiography performed four days later showed severe obstruction of the proximal left anterior descending and circumflex coronary arteries. At the time of bypass graft operation, performed three weeks later, no areas of hypokinesis were noted. Postoperatively he did well and the 12 lead electrocardiogram was normal.

Discussion

During stress testing, our patient developed transient Q waves in V1-V2 with ST segment elevation and subsequent left anterior fascicular block. No evidence confirming acute myocardial infarction was obtained.

In patients without previous myocardial infarction ST segment elevation during stress testing is considered to be indicative of Prinzmetal's angina, due to

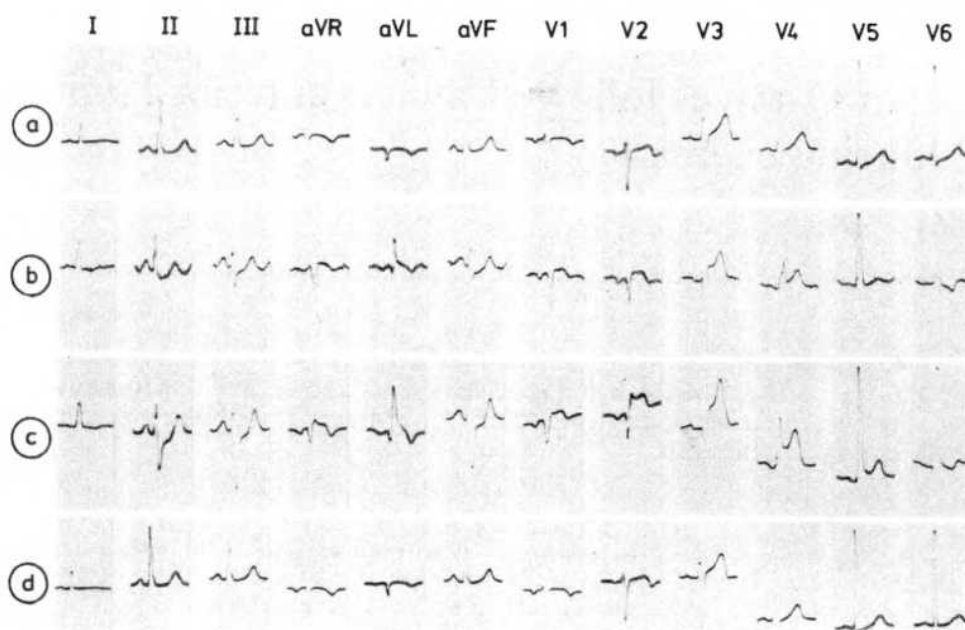


Fig. 1 (a) Resting electrocardiogram RS pattern from V1 to V3; QRS axis, $+70^\circ$. (b) During stress testing (fifth minute): QS pattern in V1 to V2; ST segment elevation from V1 to V4; QRS axis, $+30^\circ$. (c) Recovery (fourth minute): further ST segment elevation; left anterior fascicular block (QRS axis, -40°). (d) Recovery (tenth minute): reappearance of R waves in V1 to V2; disappearance of left anterior fascicular block.

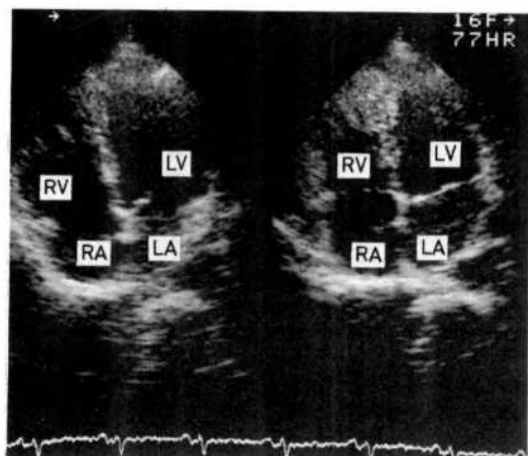


Fig. 2 Cross sectional echocardiogram in apical four chamber projection (left, diastole; right, systole), recorded at the sixth minute of the recovery period after exercise testing. No regional abnormalities in left ventricular wall motion are observed. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

severe proximal left anterior descending coronary artery obstruction, which was subsequently shown in our patient by coronary arteriography.³

Transient Q waves without acute myocardial infarction have been observed during coronary insufficiency,^{4,5} Prinzmetal's angina,³ and exercise electrocardiography.² According to the different authors, they may be explained either by electrical inertness of myocardial cells due to ischaemic alteration of the cell membrane^{6,7} or by localised conduction disturbance.^{8,9} In our patient an intraventricular conduction defect developed gradually after the appearance of Q waves; both Q waves and left anterior fascicular block disappeared simultaneously.

Transitory intraventricular conduction defects appearing during exercise testing may be rate related and not strictly dependent on the actual presence of acute myocardial ischaemia.¹⁰ In our patient the QRS axis leftward shift developed at the peak of exercise, when the heart rate was fastest. The intraventricular conduction defect, however, did not disappear but increased after stopping the test and the lowering of the heart rate; therefore a rate related intraventricu-

lar conduction defect would be unlikely.

Regional wall motion abnormalities may be detected by cross sectional echocardiography or gated blood pool scanning in the course of acute myocardial infarction or transitory acute myocardial ischaemia.¹¹ Accurate phase analysis of wall motion by both methods may provide information on the modification of the excitability sequence or the presence of conduction abnormalities during myocardial ischaemia.¹²

In our patient only qualitative inspection of the apical echocardiogram was obtained, and it did not show any appreciable abnormality of wall motion movement or synchronism.

Even though definite proof of the nature of the phenomenon here described is lacking, in our opinion the simultaneous disappearance of Q waves and left fascicular block suggests that the abnormal Q waves were due to an early conduction defect localised in the septal area (septal fascicular block),⁷ which extended eventually to left anterior fascicular subdivisions.¹³

The absence of any transitory wall motion abnormality at cross sectional echocardiography indicates electrophysiological rather than mechanical damage. Cellular inertness as the cause of the electrocardiographic sequence in our patient could not, however, be definitely excluded.

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Anomalous origin of the left coronary artery from the pulmonary artery in an adult

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SUMMARY Anomalous origin of the left coronary artery from the pulmonary artery is a rare, almost universally fatal form of congenital heart disease. A case was diagnosed in a 19 year old woman who had exercise induced syncope and ST segment displacement during exercise stress testing. The anomaly was successfully treated with ligation of the anomalous left coronary artery combined with saphenous vein grafting.

Young adults with exercise induced syncope should be examined by exercise stress testing, and if it induces ST segment displacement coronary angiography should be undertaken.

Anomalous origin of the left coronary artery from the pulmonary artery was first described by Abrikossoff in 1911.¹ About 80-90% of the reported cases of this abnormality are of the infantile type, and these patients develop congestive heart failure and die in infancy. About 15% of cases survive beyond infancy. Some of these patients die suddenly after exertion.²⁻⁴ We report an example of this condition in an adult, who underwent successful surgical treatment.

Case report

A 19 year old woman, who as a child participated in physical exercise without any symptoms, had been referred to the local hospital when 17 years old because of an episode of exercise induced syncope. Since the electrocardiogram was normal, no cardiac murmur was heard, and no neurological abnormalities were found she was discharged. Two years later she had a further episode of syncope during gymnastic exercise. Cardiac arrest occurred, and resuscitation was started during transportation to the local hospital. The electrocardiogram showed ventricular fibrillation. Direct current cardioversion resulted in sinus rhythm, and she was referred to our department for further examination.

On examination, there were some deficiencies in her memory, her blood pressure was 120/70 mm Hg, and

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Accepted for publication 26 November 1984

cardiac auscultation detected no cardiac murmurs and normal first and second heart sounds. The electrocardiogram showed a biphasic T wave in lead I but no other abnormalities. The chest radiograph suggested some left ventricular enlargement in the lateral view, but the total heart size was normal. Echocardiographic examination was normal. Exercise stress testing showed a 0.3 mV depression of the ST segment in lead CM5 but produced no chest pain. The patient was referred for right heart catheterisation and intracardiac electrography. These examinations showed no signs of left to right shunt, and no inducible ventricular tachycardia or ventricular fibrillation was recorded during electrophysiological studies. Myocardial perfusion scintigraphy with thallium-201 showed decreased activity in the anteroapical region. We therefore decided to perform coronary angiography. There was no evidence of aortic stenosis, and the pressures in the left ventricle were normal (100/8 mm Hg). Left ventriculography showed a normal contraction pattern, an ejection fraction of 0.71, no signs of mitral regurgitation, and no left coronary artery arising from the aorta. The right coronary orifice was found to be very wide and when injected with contrast was dilated and tortuous with many collateral channels through which the contrast passed to the left coronary artery and finally drained retrogradely into the pulmonary artery (Figure a).

At operation the right coronary artery was dilated. The left anterior descending artery was small with an internal diameter of 2 mm. The left anterior descending and the circumflex arteries were in the normal

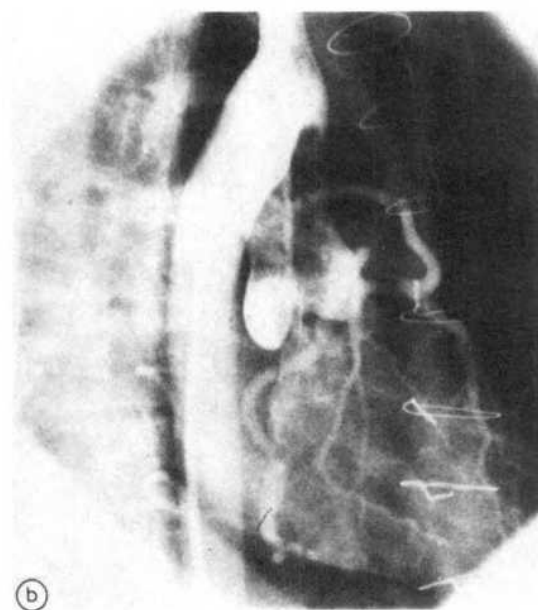
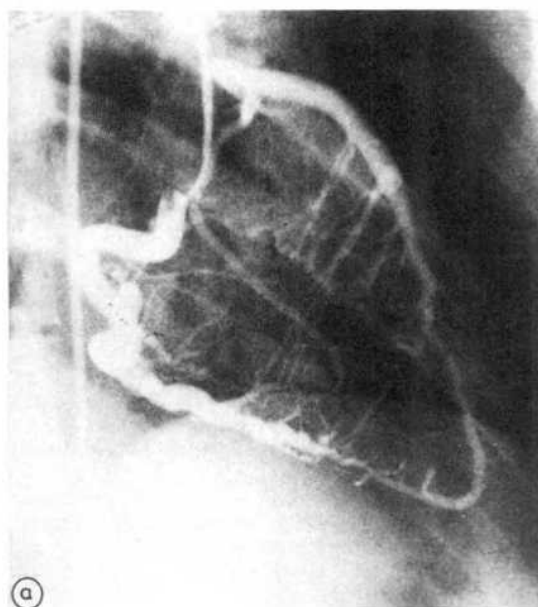


Figure (a) Preoperative coronary angiogram in the right anterior oblique projection with contrast injection into the right coronary artery showing retrograde filling of the left coronary artery and the circumflex artery. There is weak contrast filling of the pulmonary artery. (b) Postoperative angiogram in the right anterior oblique projection with contrast injection into the aorta showing contrast filling of the venous graft and the left coronary, the circumflex, and the right coronary arteries. There are no signs of contrast passing from the right to the left coronary arteries.

anatomical position, but the left main coronary artery originated from the posterior wall of the pulmonary artery. After the left main coronary artery had been dissected, it was ligated close to the pulmonary artery and divided. A piece of reversed saphenous vein was inserted between the left main coronary artery and the aorta, using an end to side suture for the peripheral anastomoses. The postoperative course was uneventful, and the electrocardiogram was unchanged.

Five months later repeat angiography showed that the right coronary artery was dilated and tortuous but there was no contrast filling of the left coronary arteries. When contrast was injected into the aorta we found a patent venous graft with contrast filling of the left anterior descending artery, the septal branches, and the circumflex artery (Figure b). The electrocardiogram still showed a biphasic T wave in lead I but no other abnormalities. The chest radiograph was normal. Exercise stress testing showed a 0.2 mV depression of the ST segment in lead CM5 of the electrocardiogram. The patient had to stop exercise because of exhaustion.

Discussion

Anomalous origin of the left coronary artery from the pulmonary artery is the most common clinically severe congenital anomaly affecting the coronary system. Nevertheless, it is a rare defect occurring in 0.5 of the total group of congenital heart disease. According to Keith it occurs in one of every 300 000 live births.⁵ Retrograde blood flow in the left coronary artery is present in probably all patients who survive childhood.⁶

Surgical treatment of this anomaly has included ligation of the anomalous left coronary artery,⁷ ligation of the anomalous left coronary artery combined with saphenous vein grafting from the aorta to the left coronary artery,^{8,9} and reimplantation of the anomalous left coronary artery in the aorta.¹⁰ Our patient was treated with ligation of the anomalous left coronary artery combined with saphenous vein grafting from the aorta to the left coronary artery.

This case is interesting because of the lack of abnormalities found at physical examination and especially because of her resting electrocardiogram, in which we would have expected to find Q waves (indicating previous anterolateral or anteroapical myocardial infarction) or alterations in the ST segments and the T waves, which have been reported by others.^{3,4,7} As reported by others we found an abnormal ischaemic response in the electrocardiogram during preoperative exercise stress testing.^{3,10}

The present case illustrates the importance of performing exercise stress testing in young adults with exercise induced syncope, even if there are no signs of

cardiac disease. It also emphasises the importance of performing coronary angiography in these patients when ST segment displacement is found at exercise stress testing.

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Correspondence

Left ventricular gradients in hypertrophic cardiomyopathy

Sir,

Sugrue *et al* (1984;52:602-9) reported that their group of eight patients with hypertrophic cardiomyopathy and mean resting gradient of 42 mm Hg did not show evidence of impedance to left ventricular emptying. This finding corroborates recent observations of systolic anterior motion of the mitral valve. At a gradient of 42 mm Hg subaortic obstruction (as demonstrated by systolic anterior motion with septal contact) would not have occurred until 40% of the way through the systolic ejection period, by which time 80% of stroke volume would have already been ejected.¹ The results of Sugrue *et al* cannot, however, be extrapolated to suggest that "a left ventricular gradient does not represent true obstruction" for two reasons. Firstly, left ventricular emptying must be interpreted in the light of the associated mitral regurgitation accompanying systolic anterior motion with septal contact. The left ventricle ejects rapidly in patients with hypertrophic cardiomyopathy, and any tendency to slow down this rapid ejection by the resulting subaortic obstruction from systolic anterior motion with septal contact may be counterbalanced by the accompanying mitral regurgitation, which will facilitate rapid emptying.² Secondly, the size of the pressure gradient is crucial in the interpretation of studies of left ventricular emptying. Thus when the pressure gradient is as high as 140 mm Hg systolic anterior motion with septal contact develops as early as 10% of the way through systole, and the resulting subaortic obstruction occurs when 93% of the stroke volume has still to be ejected.¹ Just as systolic anterior motion is not an "all or none phenomenon" so the subaortic pressure gradient is not an "all or none phenomenon." Gradients such as those in the patients studied by Sugrue *et al* do not usually suggest important left ventricular obstruction. Higher pressure gradients do suggest significant outflow obstruction as shown by prolonged ejection time,¹ fall in ejection fraction with exercise,³ and amelioration of angina when the pressure gradient is relieved.⁴

Charles Pollick,
Division of Cardiology,
Toronto Western Hospital,
399 Bathurst Street,
Toronto,
Ontario, Canada.

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This letter was shown to the authors, who reply as follows:

Sir,

Dr Pollick's comments on the influence of mitral regurgitation and of the importance of the magnitude of left ventricular gradients on left ventricular ejection are made from the perspective of his elegant work which demonstrates a strong positive correlation of the duration of systolic anterior motion, the left ventricular ejection time, and the magnitude of left ventricular gradient in patients with muscular subaortic stenosis.¹ These patients are a subset of the spectrum of hypertrophic cardiomyopathy—namely, those with an idiopathic heart muscle disorder which is characterised by a hypertrophied and non-dilated left ventricle.^{2,3} In such patients left ventricular gradients may or may not be observed, and their presence is associated not only with systolic anterior motion but with other mechanisms that are not associated with mitral regurgitation.

As stated, the patients in our study did not have moderate or significant mitral regurgitation. In our large series of patients with hypertrophic cardiomyopathy 35% had a resting left ventricular gradient of between 30 and 120 (median 45) mm Hg and patients with a gradient in excess of 80 mm Hg were rare (<10%). Our findings are relevant to the majority of patients with hypertrophic cardiomyopathy who have a resting left ventricular gradient. We have sub-

sequently compared the proportion of stroke volume ejected during the various phases of systole in 11 patients with resting left ventricular gradients of 50–120 (median 80) mm Hg and patients without resting or provokable gradients who were matched for age, sex, and ejection fraction. The initial third, the initial 50%, and the initial 80% of systole were similar in those with and without left ventricular gradients. These findings support our conclusion that a left ventricular gradient does not represent true obstruction.

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- 3 Goodwin JF. The frontiers of cardiomyopathy. *Br Heart J* 1982;48:1–18.

Notices

Cardiac Doppler

An international congress on cardiac Doppler will be held in Pisa from 14 to 18 October 1985. Further details may be obtained from Dr Alessandro Distanti, Istituto di Fisiologia Clinica, CNR, Università di Pisa, Via Savi 8, I-567100 Pisa, Italy.

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts will be 2 January 1986.

Correction

In the paper by Fioretti *et al* (1985; 53: 248–52) on the “Limitations of a QRS scoring system to assess left ventricular function and prognosis at hospital discharge after myocardial infarction” the curves for ejection fraction and QRS score in Fig. 3 should have been represented by a continuous line (——) and a broken line (— — —) respectively.

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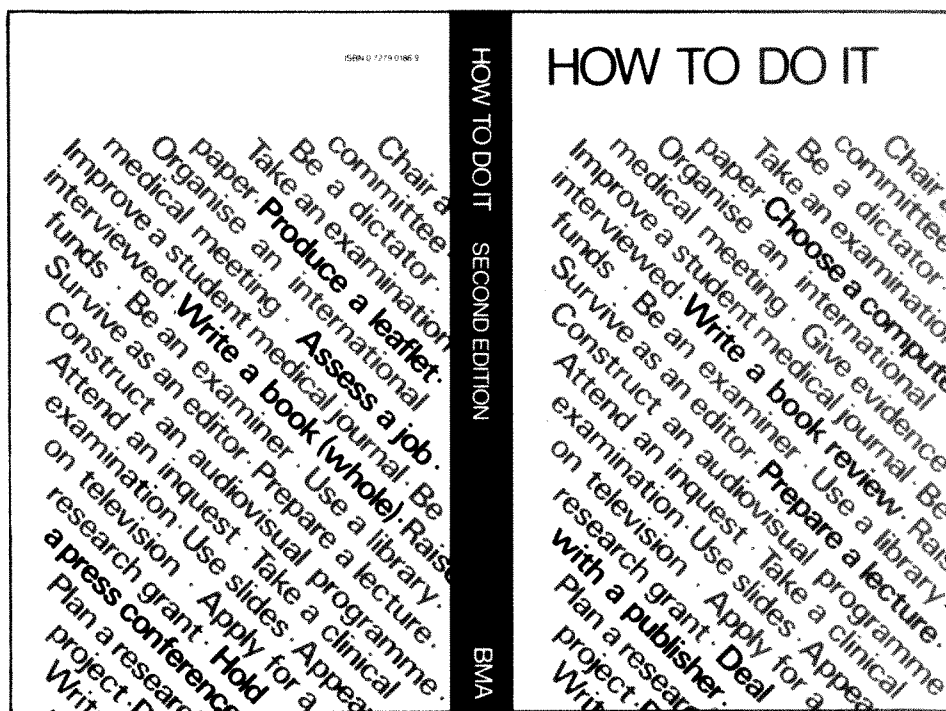
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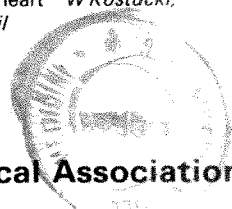
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Editorial: the challenge and the reproach of infective endocarditis <i>J F Goodwin</i>	115	Prevalence and clinical significance of aortic valve prolapse <i>L M Shapiro, B Thwaites, C Westgate, R Donaldson</i>	179
Editorial: do we need a new standard for electrocardiographs? <i>R G Gold</i>	119	Embolisation procedures in congenital heart disease <i>J F Reidy, O D H Jones, M J Tynan, E J Baker, M C Joseph</i>	184
Artefactual ST segment abnormalities due to electrocardiograph design <i>D I Tayler, R Vincent</i>	121	Functional and anatomical correlates in atrial septal defect: an echocardiographic analysis <i>J C Forfar, M J Godman</i>	193
Acute coronary occlusion during percutaneous transluminal coronary angioplasty <i>M F Shiu, N P Silverton, D Oakley, D Cumberland</i>	129	Left ventricular outflow tract obstruction in complete transposition of the great arteries with intact ventricular septum: a cross sectional echocardiographic study <i>P J Robinson, R K H Wyse, F J Macartney</i>	201
Effect of smoking habits and timolol treatment on mortality and reinfarction in patients surviving acute myocardial infarction <i>P K Rønnevik, T Gundersen, A M Abrahamsen</i>	134	Non-invasive assessment of pulmonary blood supply after staged repair of pulmonary atresia <i>S del Torso, M J Kelly, V Kalff, G Stellin, R B B Mee, A W Venables</i>	209
Role of transient ischaemia and perioperative myocardial infarction in the genesis of new septal wall motion abnormalities after coronary bypass surgery <i>P Ribeiro, P Nihoyannopoulos, S Farah, D W Moss, S Westaby, C M Oakley, R A Foale</i>	140	Case reports	
Does left ventricular aneurysmectomy improve ventricular function in patients undergoing coronary bypass surgery? <i>N C Taylor, R Barber, P Crossland, E P Wraight, T A H English, M C Petch</i>	145	Spontaneous recanalisation of side branches occluded during percutaneous transluminal coronary angioplasty <i>M F Shiu, A Singh</i>	215
Prevalence of overt dilated cardiomyopathy in two regions of England <i>D G Williams, E G J Olsen</i>	153	Fluid removal by haemofiltration in diuretic resistant cardiac failure <i>S H Morgan, M A Mansell, F D Thompson</i>	218
Familial right ventricular dilated cardiomyopathy <i>H H W Ibsen, U Baandrup, E E Simonsen</i>	156	Permanent pacemaker failure due to surgical emphysema <i>S A Smith, P L Weissberg, L - B Tan</i>	220
Plasma free captopril concentrations during short and long term treatment with oral captopril for heart failure <i>T R D Shaw, F M Duncan, B C Williams, E Crichton, S A Thomson, J R E Davis, M Rademaker, C R W Edwards</i>	160	Chronic nicotine ingestion and atrial fibrillation <i>P M Stewart, J R Catterall</i>	222
Role of echocardiography in differential diagnosis of broad complex tachycardia <i>C Wren, R W F Campbell, S Hunter</i>	166	Changing echocardiographic features of a hydatid cyst of the heart <i>W Kostucki, M van Kuyk, A Cornil</i>	224
Interrelation between donor and recipient heart rates during exercise after heterotopic cardiac transplantation <i>S Yusuf, A Mitchell, M H Yacoub</i>	173	Correspondence	226
		Notices	226

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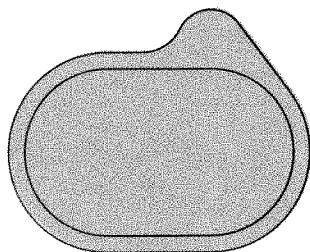
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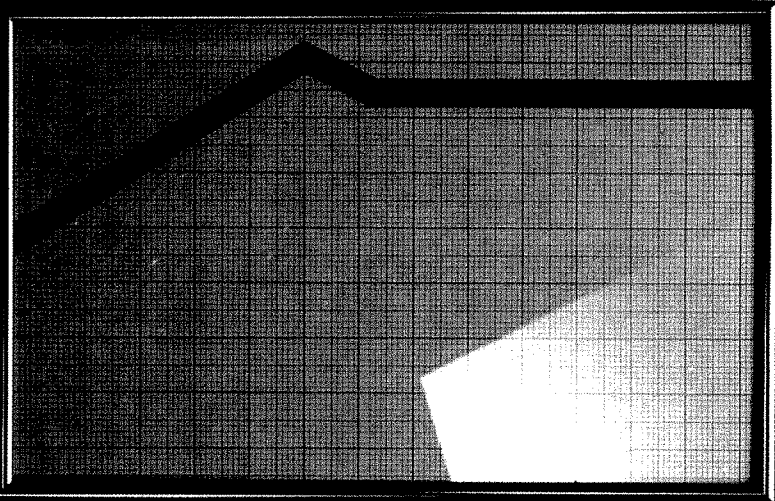
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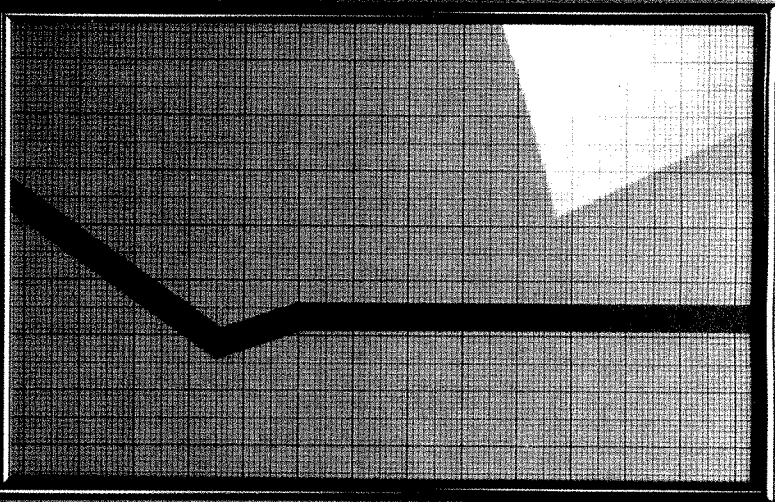
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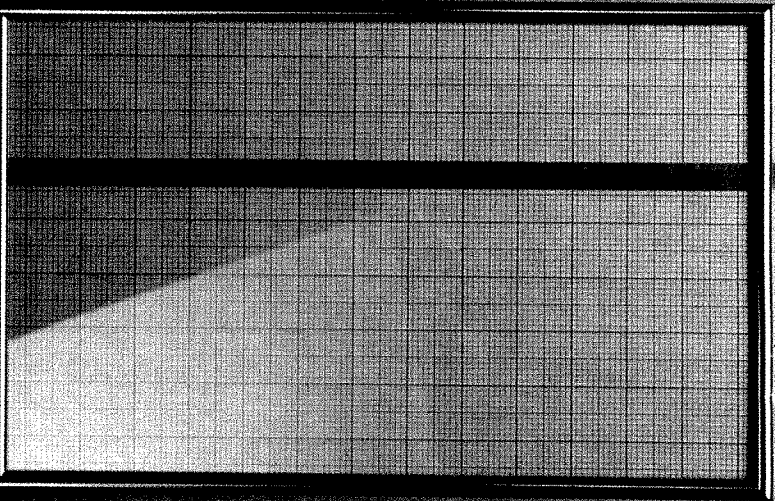
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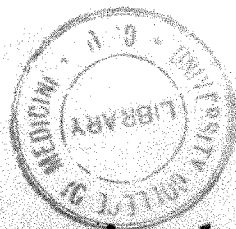
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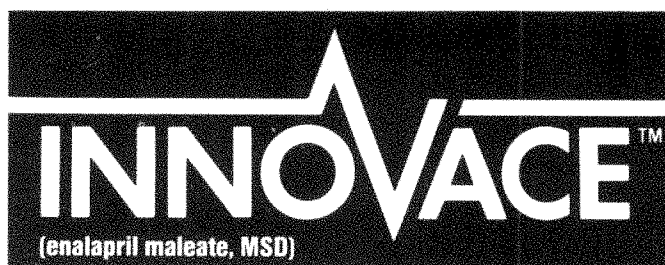
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Renovascular hypertension: 'Innovace' can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 'Innovace' is dialysable.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

DRUG INTERACTIONS

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SIDE EFFECTS

Generally well tolerated. Most side effects mild and transient, and have not required discontinuation of therapy. Most frequently: dizziness, headache, fatigue, asthenia. Others include hypotension, orthostatic hypotension, nausea, diarrhoea, muscle cramps, rash, cough, dysgeusia, and angioneurotic oedema. With minor and transient rises in blood urea or creatinine, dosage reduction and discontinuation of 'Innovace' and/or the diuretic may be required.

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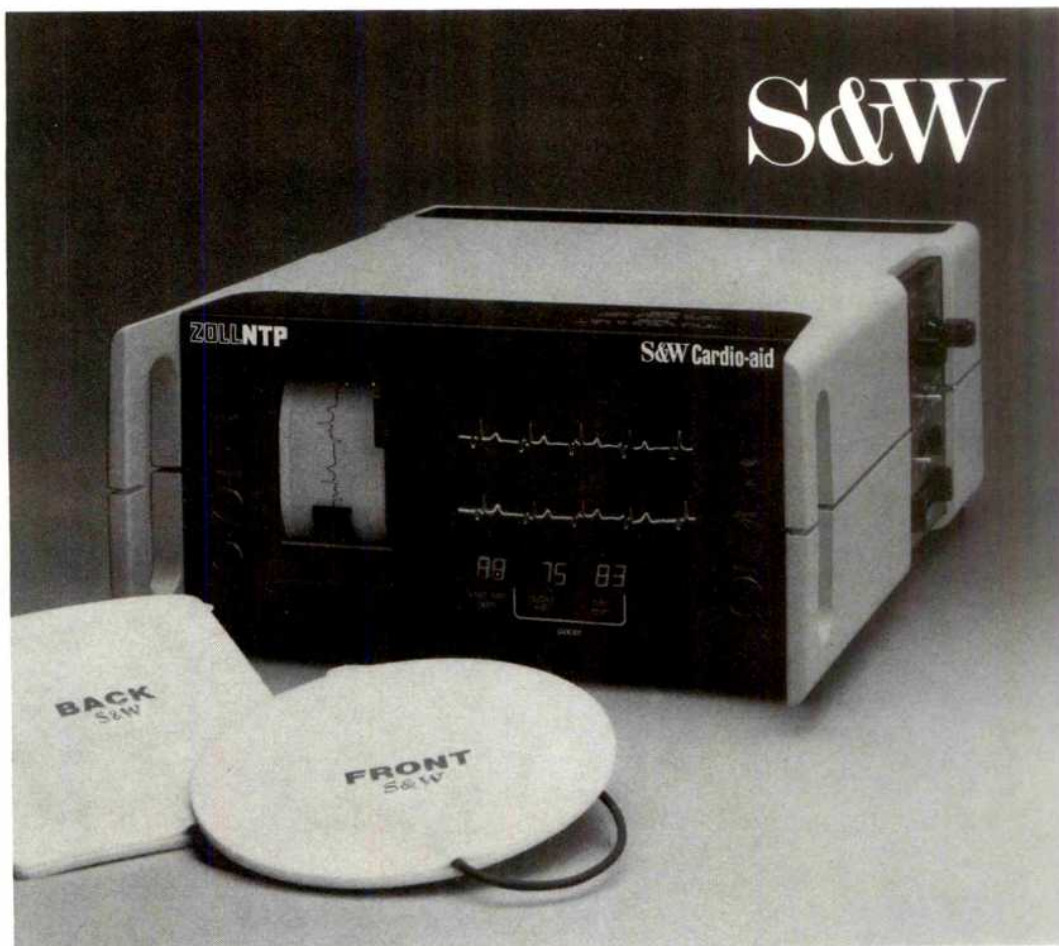
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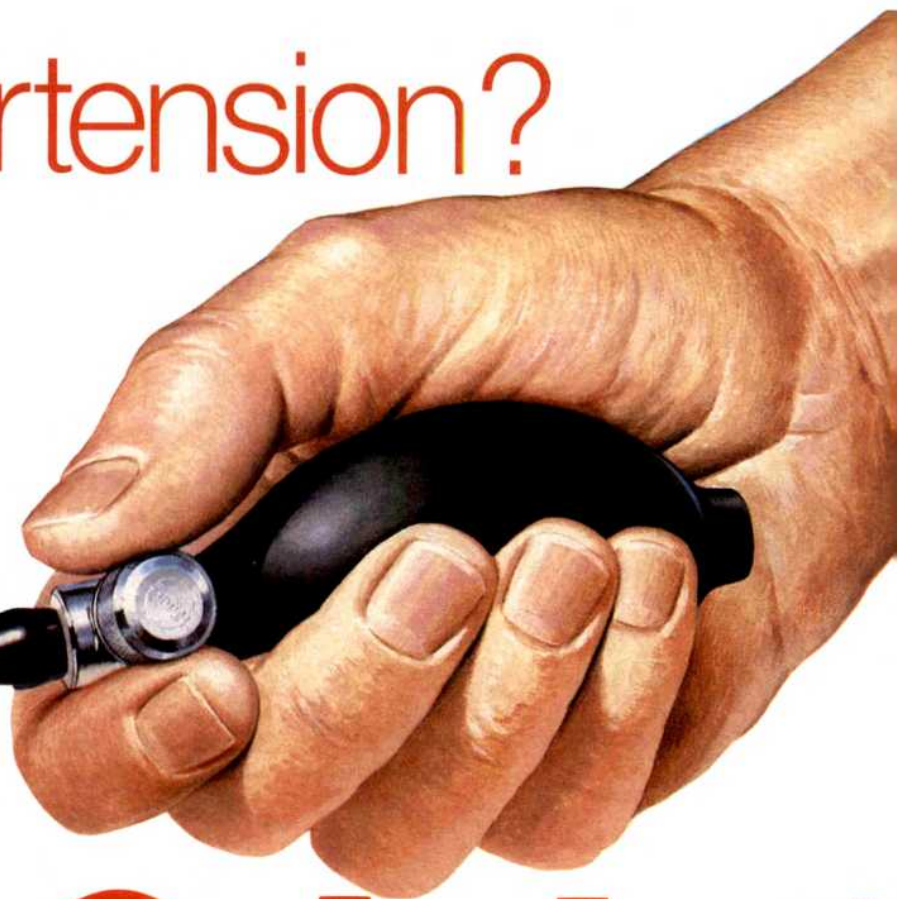
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Editorial

The challenge and the reproach of infective endocarditis

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Bacterial endocarditis, or as it is better and more comprehensively termed infective endocarditis, has long been clearly recognised. Osler¹ and Horder² amplified the original descriptions, and in 1909 Osler commented on the chronic form of the disease. Infective endocarditis was fatal in virtually all patients until the introduction of penicillin. Only 4-6% of patients responded to sulphonamide, which was given before the introduction of penicillin. After its introduction mortality fell from almost 100% to 30%, and there the rate has generally stayed,^{3,4} though lower figures have been quoted from major centres.⁵ The probable increase in the incidence of the disease,⁶ however, tends to offset any fall in mortality in the past decade. The age distribution of patients with infective endocarditis has changed during the past 50 years; the mean age has increased from 32 to 50 years or more, and the disease has become increasingly common in 60-80 year old subjects.

Although the incidence of rheumatic valvar disease has fallen substantially in developed countries, the pattern of infective endocarditis has not changed appreciably. A recent survey of the Medical Services Study Group of the Royal College of Physicians of London associated with the British Cardiac Society has provided information on 541 patients in the United Kingdom who developed infective endocarditis during the years 1981-82.⁷⁻⁹ The mean age was 51, the commonest primary cardiac disorder was rheumatic (in 126 patients), and the commonest organism isolated was *Streptococcus viridans*. Of the 541 patients, 171 had no history of heart disease. The mortality was 30% for staphylococcal infections and 6% for streptococcal infections, but cultures from 54 patients (10%) yielded negative results.

Reasons for the apparently increasing incidence of infective endocarditis could be the development of

infection on prosthetic valves and other materials introduced into the heart and the recognition of unusual forms of infective endocarditis such as coxiella (Q fever), chlamydia (psittacosis), and fungal infections. Fungal infections may paradoxically have increased as a result of more intensive and lengthy chemotherapy for advanced bacterial infective endocarditis.

Patients who are immunologically compromised such as those taking immunosuppressive drugs are especially vulnerable to infection of any sort. Infective endocarditis due to self injection without aseptic precautions by drug addicts can be a serious source of infective endocarditis but is fortunately uncommon in the United Kingdom.

With the development of more powerful antibiotics, improved diagnostic methods such as cross sectional echocardiography, and increased awareness of the problems, why is the mortality so high? If infective endocarditis is curable, why is it not cured more often? As no simple answer is readily forthcoming attention has focused again on prophylaxis. Who should be protected and how? What is the value of prophylaxis? In the survey by the Medical Services Study Group 19% of infections were thought to be dental in origin, but in only 76 of the 544 episodes (14%) of infective endocarditis had a dental procedure been performed within three months of presentation. Organisms of the *S viridans* group were the cause of infection in 33 patients who had dental sepsis but who had not been treated recently. Organisms from the gastrointestinal tract were also isolated, often in connection with operations, investigations, or disease of the alimentary tract.

Prophylaxis

Prophylaxis, therefore, is important during dental work, gastrointestinal tract procedures, and genitourinary investigations. An awareness of the need to

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maintain good dental hygiene is most important, especially in patients with cardiac disease. The regularity of infection with *S. viridans* has emphasised the importance of prophylaxis during dental work, but *S. viridans* can be found in parts of the body other than the mouth or pharynx, while bacteraemia can occur from dental sepsis without any dental work precipitating it, as in the patients in the Medical Services Study Group's survey who developed *S. viridans* endocarditis without recent dental attention. Prophylaxis during dental work is not strikingly effective, but, nevertheless, cannot be neglected. There could be many reasons for its relative ineffectiveness: penicillin is not given or is improperly given; susceptible patients are not identified; or no prophylaxis is given at all to susceptible patients. If all these aspects are to be dealt with who then should be given prophylaxis? Obviously those with known cardiac defects must have prophylaxis, but it is important to know which defects are especially susceptible to infection—that is, those that are concerned with pronounced mechanical stress, especially when blood is driven from a high pressure source through a narrow orifice into a low pressure segment.¹⁰ Thus patients with mild mitral regurgitation, bicuspid aortic valve, ventricular septal defect, and persistent ductus arteriosus are characteristically vulnerable to infection, while those with a low cardiac output, pronounced valve regurgitation, and severe heart failure are less so. At the end of the spectrum is the secundum atrial septal defect, in which infective endocarditis is virtually unknown. Nevertheless, some patients with atrial septal defect have mitral valve lesions that can readily become infected.

The simple answer would be to protect everyone with any suggestion of cardiac disease, and this is often done. Since infection can occur on a normal valve, however, or at least in patients not known to have cardiac disease, should everyone be given dental prophylaxis? Even if this was practicable, would the hazard of penicillin reaction outweigh the benefits? Possibly they would, but the survey by the Medical Services Study Group inclines to the view that perhaps all patients over the age of 60, even without evidence of cardiac disease, should be given prophylaxis. This is a valuable suggestion because of the increase in infective endocarditis found in older patients and the risk of infection from instrumentation of the gastrointestinal and genitourinary tracts that is common in elderly people.

The recommendations of the Medical Services Study Group and the British Society for Antimicrobial Therapy generally agree on the means of prophylaxis¹¹: for dental work in outpatients 2 g amoxycillin should be given by mouth one hour before the work is carried out: for inpatients penicillin

can be injected intramuscularly: for patients undergoing instrumental procedures on the lower gastrointestinal and genitourinary tracts ampicillin or amoxycillin combined with gentamicin should be given—a single dose should cover investigations; and for patients sensitive to penicillin erythromycin is advised.

Treatment

Since over 80% of infections are due to staphylococci or streptococci initial treatment should be with a combination of drugs such as gentamicin and penicillin. Benzylpenicillin should be given for streptococci likely to have come from the mouth; flucloxacillin for staphylococcal infections; and ampicillin for faecal streptococci.¹² Treatment should be given intravenously, preferably by a central subclavian line inserted under full aseptic conditions. The line can be left in position for several weeks, but specimens from the tip should be cultured on removal. A regular weekly injection of amphotericin to prevent secondary fungal infections is useful. The duration of treatment should be not less than four weeks—six weeks for complicated cases and prosthetic valve infections. The dose of benzylpenicillin should be not less than 10 MU daily; some authorities recommend 20 MU daily but this carries some risk of penicillin complications such as convulsions and hyperkalaemia. Low dose heparin (1 U/ml) added to the infusion fluid limits the risk of the formation of thrombi. If heart failure is present, or deemed likely, sodium penicillin should be avoided. The intravenous route should be continued for a minimum of two weeks, preferably three, and then penicillin may be given orally. Treatment with gentamicin must be monitored by blood concentrations. Peak concentrations should not exceed 14 mg/l or fall below 5 mg/l. Trough concentrations should not exceed 2 mg/l.

Special problems of treatment include prosthetic valve endocarditis, endocarditis in drug addicts, fungal endocarditis, and coxiella endocarditis. Prosthetic valve endocarditis occurs either early in the postoperative phase, within two months of operation, or late: early endocarditis is usually due to the entry of staphylococci into the blood from the skin of the patient,¹³ which often occurs when surgical drains are removed from the chest. During this manoeuvre antistaphylococcal chemotherapy should be given. The prognosis of early endocarditis treated medically is much worse than that of late endocarditis.¹⁴ Westaby *et al* reported 21 patients who suffered 25 attacks of prosthetic valve endocarditis.¹⁵ Nine patients with late prosthetic valve endocarditis were cured by medical treatment alone, two died before operation was possible, and 11 required replacement of prosthetic

valves after treatment with antibiotics. Three patients died and two needed replacement of their valves after medical treatment.

Surgical treatment is thus often needed for prosthetic valve endocarditis, and constant vigilance is necessary to detect infection early and begin effective medical treatment. If, despite this, infection continues, embolism occurs, or vegetations damage the prosthetic valve further operation should not be delayed. The diagnosis should be suspected if there is unexplained fever, heart failure, embolism, change in the auscultatory characteristics of the prosthetic valve, or persistent anaemia due to mechanical haemolysis. In view of the echoes produced by the metal parts of the valve echocardiography (especially M mode) is of only limited value in diagnosis, but changing patterns of the structure of the valve on repeat examination may be of some help.

Surgical treatment is most important also for native valvar endocarditis, and should be considered in any patient who shows evidence of pronounced valve failure, conduction defects, or embolism and does not respond immediately to medical treatment. Delay in surgical treatment can be disastrous, although operation in the face of continuing infection is no bar to success, in fact the reverse. The need for replacement of valves is particularly great in infections noted for the severe destruction of valves, particularly staphylococcal, coxiella, and fungal infections. Medical treatment practically never cures coxiella endocarditis, and fungal endocarditis, which carries a high mortality, is difficult to treat medically because antifungal drugs (amphotericin B and 5-fluorocytosine) are fungistatic rather than fungicidal and are toxic to the patient.

Delay in diagnosis

When so much time and effort has been put into the prevention, detection, and treatment of infective endocarditis, where lies the reproach? It lies in the failure to reduce mortality appreciably below 30%. Reasons for the failure are multiple and include organisms resistant to antibiotics; more direct exposure of the heart to infection by open operation, and insertion of foreign bodies into it; and older and sicker patients who develop the disease. Probably the most important impediment to good results, however, is late diagnosis. Ranged against these hazards are improved antibiotics and effective surgical treatment for infective endocarditis. Why then have these advances not had an effect on mortality? The answer lies both in the continued delay in diagnosis and in the failure to consult the cardiac surgeon in the early stages of the disease. Diagnosis is delayed because infective endocarditis is a great mimic; it can be hidden by many other

cardiac diseases that it inhabits and can counterfeit many medical diseases, notably renal disease, disease of the connective tissue, and cerebral vascular disease to name a few. Evidence of infection in the early stages may consist of no more than unexplained malaise, anaemia, the insidious development of heart failure for no known cause, rheumatic aches and pains, or even psychoneurosis.

Reliance on special investigations rather than on repeated careful clinical examinations can cause confusion—for example, echocardiography, which is probably the single most important investigation, can be abused if it is wrongly applied. A request for "echocardiogram please to exclude subacute bacterial endocarditis" is to be deprecated. If no vegetations are seen and the report is negative then the possibility of the diagnosis may be erroneously put aside and valuable time lost. Whenever possible, cross sectional as well as M mode echocardiography should be used.

Recommendations

All that has been said is well known to cardiologists and to most readers of the *British Heart Journal*. Why say it then? My purpose is to appeal to those outside cardiology: patients, dental surgeons, general surgeons, gastrointestinal surgeons, genitourinary surgeons, general practitioners, and consultant physicians for the best available prophylaxis and the earliest possible diagnosis and treatment. Although prophylaxis remains a somewhat imprecise exercise, it should at least be meticulously applied to patients who are especially at risk. Early diagnosis can be greatly helped if, when any patient with known heart disease develops a fever of unknown cause that lasts for more than a few days, blood cultures (or if not possible an erythrocyte sedimentation rate and haemoglobin estimation) are performed before any antibiotics are given. This reduces the risk of damping down the infection temporarily and rendering results of subsequent blood cultures negative. The possibility of infective endocarditis should be considered in any cardiac patient who becomes mysteriously unwell, develops heart failure, arrhythmia, heart block, or, most obvious of all, a new cardiac murmur. Patients with known heart disease should be told about infective endocarditis and how to reduce the risk: they should be asked to be meticulous in prophylactic measures and report to their general practitioner for a blood test if they develop unexplained fever or malaise.

General practitioners should be encouraged to think always of the possibility of infective endocarditis in patients with heart disease, to take the necessary blood tests when indicated before giving antibiotics, and if in doubt to refer the patient to a specialist.

The consultant physician can further the cause of early diagnosis and successful treatment by repeated meticulous clinical examination; by applying echocardiography shrewdly; and by bearing in mind the possibility that surgical treatment may be needed, not as a last resort but as a planned procedure complementary to chemotherapy. Valves that become severely damaged over a short time cause important defects of myocardial function that can seriously worsen prognosis, while uncontrolled infection can burrow malignantly into the great vessels producing aneurysms and deep into the heart causing serious conduction defects.

The combination of enhanced awareness on the part of the patient, the general practitioner, and the physician, together with meticulous prophylaxis, early consultation with the cardiac surgeon, and effective treatment with antibiotics should appreciably reduce the mortality. The challenge must be accepted and the reproach neutralised.

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Editorial

Do we need a new standard for electrocardiographs?

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Since their publication in 1975, the recommendations of the American Heart Association Committee on Electrocardiography¹ have been adopted widely as an unofficial international standard for the performance of electrocardiographs. More recently the draft standard of the International Electrotechnical Commission for performance requirements for single channel and multi channel electrocardiographs² has provided an alternative but again unofficial international standard with which many manufacturers, particularly in Europe, now comply.

One of the main differences between these two standards concerns the specifications laid down for the frequency response of the electrocardiograph. The International Electrotechnical Commission draft demands that the response of the electrocardiograph at 75 Hz shall be between 71% and 105% of the response at 10 Hz and that between 0.5 Hz and 60 Hz the response shall be 90-105% of the response at 10 Hz. The low frequency performance (below 0.5 Hz) is determined by the requirement that after the application of a step function input signal the decay of the recorded amplitude for the first 360 ms shall not exceed that produced by a time constant of 3.2 s. The American Heart Association specification is somewhat more strict. For the high frequency performance the response at 100 Hz is specified rather than that at 75 Hz. The amplitude of the electrocardiograph record at 0.05 Hz must be not less than 70% of the amplitude at 10 Hz and should be substantially constant down to a frequency of 0.14 Hz. In neither of these standards is there any reference to phase response.

Taylor and Vincent have drawn attention to the importance of phase linearity at low frequency in the performance of electrocardiographs.³ In their care-

fully documented study reported in this issue (p 121) they have shown the artefactual ST changes that can be introduced into the electrocardiogram by a non-linear phase response. The distortion was greatest in the presence of large T waves and ST segment elevation or depression. Low frequency phase delays produced early ST segment elevation and terminal T inversion in leads with a dominant S wave and horizontal ST depression in leads with a dominant R wave. The changes noted were similar to those seen in disease states and could easily give rise to a false diagnosis of ischaemic heart disease. Furthermore, such changes could be produced by an electrocardiograph that complied with the rigorous American Heart Association frequency response specifications. Now that these phase errors can be substantially reduced by modern filtering techniques, Taylor and Vincent very reasonably suggest that the International Electrotechnical Commission draft specification should be changed to incorporate requirements for phase response.

Many cardiologists are all too familiar with the "built-in ST depression" inherent in the tracings produced by some of the early direct writing electrocardiographs. Taylor and Vincent remind us that less blatant errors may occur with modern equipment and that we still do not have a British standard nor an international standard for electrocardiograph performance. It is 10 years since Krnkler and MacFarlane⁴ made a strong plea for a "meaningful international standard" for electrocardiograph performance prepared in consultation with cardiologists and their scientific colleagues. This standard has not yet been forthcoming. The second version of the draft standard on performance requirements for single and multi channel electrocardiographs was considered by a panel of the British Standards Institution in February 1977 and was distributed to the member nations of the International Electrotechnical Commission in June 1978. Only 14 of the 19 member countries had replied within the six month period given for voting and the

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last reply was not received until October 1979. Eighteen countries voted in favour of the draft but the United States rejected it, the main technical objection being to the less stringent frequency response requirements of the International Electrotechnical Commission document. One negative vote from among the 19 member countries would not have prevented a draft from proceeding to its next stage and at a meeting in Washington of subcommittee 62D of the International Electrotechnical Commission it was agreed that a revised draft would be circulated under the "2 month procedure."

Meanwhile in 1977 the International Electrotechnical Commission published the first part (general requirements) of its standard for safety of medical electrical equipment.⁵ This was subsequently issued as British Standard 5724, part 1 1979,⁶ which is now the recognised official standard in the United Kingdom for the safety of medical and electrical equipment. Part 2 of this standard considers the particular requirements necessary for different groups of medical electrical equipment and several of these particular standards have already been published. The draft standard on the requirements for the safety of electrocardiographs was circulated to national committees in April 1981 for voting on within six months. In June 1981 a meeting of subcommittee 62D of the International Electrotechnical Commission decided to give priority to the preparation of such particular safety standards, and work on the standard for the performance of electrocardiographs was shelved. The standard for the safety of electrocardiographs was approved by 17 countries but was rejected by the United States and Canada. It was therefore resolved that the particular standard for the safety of electrocardiographs should be published as an International Electrotechnical Commission standard.

At the time of writing the safety standard has not yet appeared and work on the standard for the performance of electrocardiographs, now seven years overdue, remains at a standstill. During this time considerable advances have been made in electronic techniques and the comments of Tayler and Vincent are therefore timely.

Even allowing for the complexities of drawing up an international standard with 19 participating countries, the delay since work on the draft performance standard was started seems inexcusably long. The result is that there is still no British standard for electrocardiograph performance. Perhaps the pursuit of an international standard is utopian. A strong case can be made for a European standard. Channels for the formulation of such a standard already exist in the form of European Committee for Electrotechnical Standardisation (Cenelec) and the technical content of the international draft has already been agreed by all of the member nations from Europe. Although a

British standard is not usually issued until the international counterpart has been published, there is precedent for such a standard to be issued in advance of international publication. Several countries already have their own national standard and a strong case can be made for the early publication of a British standard for performance. This would not preclude revision of such a standard when an international standard is published.

No matter how rigorous the standard for the design and manufacture of an electrocardiograph, the user still largely determines the quality of its performance. Too often deterioration of instruments passes unrecognised and even when electrocardiographs are working properly they may be so misused that a reliable tracing cannot be obtained.

All too often, rather than spend time in relaxing a tense patient, the technician resorts to the use of the filter to provide a tidy looking trace but one in which a small initial R wave can be obliterated, with the result that it is misinterpreted as a QS complex. Although many, but by no means all operators include the calibration signal in the record, it is seldom used as a quick means of checking the frequency response of the machine. If the calibration button is held down for three or four seconds both the high frequency and low frequency responses of the electrocardiograph can be checked.

Despite the absence of an official standard much can be done to raise the quality of electrocardiograph records, both in hospital and particularly in general practice, by regular inspection and servicing of the instruments to ensure that they are still working to the original specification (something which no British standard can ensure) and by proper training of the operator in recording techniques.

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Artefactual ST segment abnormalities due to electrocardiograph design

D I TAYLER, R VINCENT

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SUMMARY Specifications recommended for electrocardiographs omit any reference to phase characteristics and place undue emphasis on an extended amplitude response. This does not, however, ensure faithful reproduction of the electrocardiogram and may result in less effective attenuation of unwanted noise than can be achieved with modern filters. The separate effects of phase and amplitude response on electrocardiographic signals were compared, and it was shown that distortion of the electrocardiogram by equipment with an inadequate phase response may cause changes resembling those seen in ischaemic heart disease. Case reports are presented in which distortion produced by commercial equipment impeded diagnosis. Specifications recommended as standard for electrocardiographs should be modified to include phase response and allow greater attenuation of frequencies below 0.5 Hz.

The surface electrocardiogram is derived from signals that are small, complex, and often contaminated with electrical noise. Recording devices must include amplifiers and filters, but both may produce unwanted distortion unless carefully designed.

Although the electrocardiogram is a complex signal of irregular shape, it is usually repetitive. It may therefore, like any repetitive signal, be expressed as the sum of a series of simply related sine waves (Fig. 1(a)). If it is to be recorded without distortion its component sine waves must be amplified equally—that is, a machine must have an unvarying (or flat) amplitude response over the range of frequencies present in the signal. This alone, however, does not ensure faithful reproduction. It is also necessary that all components passing through the recorder should be delayed by the same amount. An equal delay of all component sine waves is achieved when the machine has a linear phase response over the required frequency range. If the phase response is non-linear components of the QRS complex will be delayed selectively and distortion will result.

Filters can be used to eliminate noise without introducing distortion only if the frequency spectrum of the noise differs substantially from that of the

signal. An ideal filter attenuates noise considerably but has no effect on signals in the required passband. Baseline drift and respiratory artefact are at lower frequencies than the electrocardiogram. Muscle tremor has a range of frequencies overlapping the wanted signal, and a power line noise has a frequency that is higher than many contained in the electrocardiogram. Thus power line noise and baseline drift may be reduced or eliminated by filtering whereas muscle tremor can be reduced only slightly.

To define standards for the design of amplifiers and filters we investigated separately the effects of an imperfect amplitude response and a non-linear phase response on normal and abnormal tracings. We also analysed the electrical characteristics of several commercially available electrocardiographs and monitors to show that equipment in routine clinical use may fail to meet these standards and may prevent accurate diagnosis.

Methods and results

Four methods were used to investigate the effects of a restricted amplitude response and phase non-linearity on electrocardiographic recordings.

Method 1—The constituent frequencies of 50 normal electrocardiographic signals were obtained using Fourier analysis. The effect of different filters on these signals was then simulated by changing the amplitude of individual frequencies or introducing phase

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Accepted for publication 2 April 1985

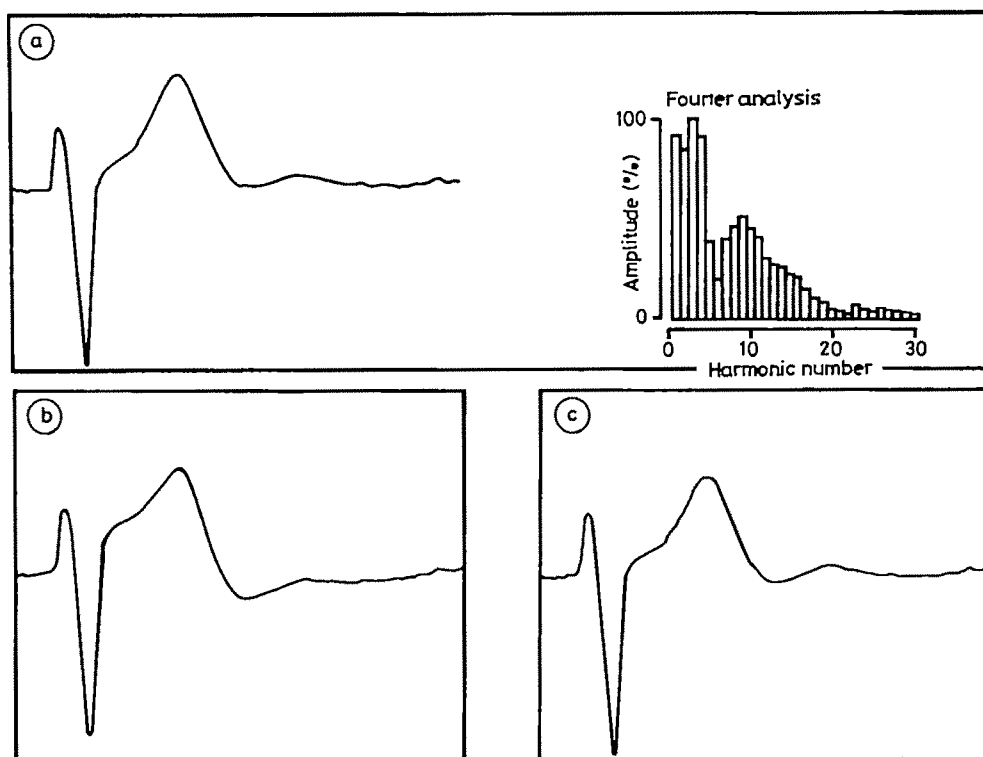


Fig. 1 (a) A typical electrocardiographic complex together with its Fourier analysis. If the heart rate is 60 beats/min then harmonic no 1 corresponds to a sinewave of 1 Hz, no 2 to 2 Hz, etc, up to 30 Hz. (b) The same complex with delayed low frequency components (note ST segment elevation). (c) The same complex with a 20% attenuation in amplitude at 1 Hz and a 10% reduction at 2 Hz. Little change in shape results, just a smaller T wave.

delays before reconstructing each waveform from its components.

Method 2—A circuit with an ideal amplitude response but a non-linear phase response (an all pass filter) was constructed to investigate the distortion of the electrocardiogram caused by phase non-linearity alone.

Method 3—The phase and amplitude characteristics of three ambulatory recorders, two electrocardiographs, and one monitor and recorder available commercially were determined, and the resulting signal distortion was noted.

Method 4—The recorders of two machines under study were modified by improving their phase response to reduce the distortion.

FOURIER ANALYSIS AND COMPUTER MODELLING (METHOD 1)

As the electrocardiogram is a repetitive signal it may be regarded as a Fourier series or the sum of a series of sine waves related harmonically.¹ We estimated the

size of the individual sine waves forming 50 different electrocardiograms by breaking each waveform into its components using a fast Fourier transform algorithm and a microcomputer. A typical electrocardiographic waveform (lead V2) together with its Fourier analysis is shown in Fig. 1(a). The lowest frequency present is the reciprocal of the RR interval. T wave information is also of low frequency, < 10 Hz, and the QRS complex has most of its energy in frequencies below 30 Hz.

After transforming the waveforms into their frequency components we were able to investigate the effect of filtering on the original electrocardiogram by changing the magnitude and delay (or relative phase angle) of individual harmonics or groups of harmonics. Once modified, the frequency components were reassembled using the microcomputer and the results compared with the original waveform (Figs. 1(b) and 1(c)).

Phase delays of the lower frequency components caused errors, predominantly in the ST segment. As

the ST segment is particularly important for the diagnosis of ischaemic heart disease we divided it into four and measured the mean and maximum distortion for each section. The amount of distortion produced depended on the degree of non-linearity introduced and the amplitude of the low frequency harmonics in the original signal. Waveforms with large T waves and ST segment elevation or depression were distorted more than waveforms with small T waves and isoelectric ST segments. Low frequency delays (or phase lags) produced early ST segment elevation and terminal T wave inversion in leads with a dominant S wave—for example, the anterior chest leads (Fig. 1(b))—and plane ST segment depression in leads with a dominant R wave.

In contrast, the waveform was insensitive to changes in amplitude response and attenuation of low frequency components without phase changes resulted only in a loss of T wave amplitude. An attenuation of 20% in amplitude of the first harmonic caused less than 0.05 mV distortion (Fig. 1(c)).

THE ALL PASS FILTER (METHOD 2)

The independent effect of phase and amplitude response was also shown by passing electrocardiographic signals through an "all pass" filter. This device had a uniform amplitude response but a non-linear phase response, passing low frequencies with a longer delay than high ones. When incorporated into the electrocardiograph this circuit produced ST changes resembling those of myocardial injury (Fig. 2). The modified machine still met the American Heart Association's specification for the frequency response of electrocardiographs.

PHASE RESPONSE OF COMMERCIALLY AVAILABLE MACHINES (METHOD 3)

We evaluated the phase and amplitude characteristics of three ambulatory recorders, two electrocardiographs, and one defibrillator/monitor, which had been modified by the manufacturer to perform a 12 lead electrocardiogram.

The amplitude response of a hard copy electrocardiographic recorder is easy to determine: a sine wave of variable frequency but fixed magnitude (1 mV peak to peak) may be applied to the input of the device and the usual pen recorder used to draw the output on paper. The relative amplitude of the inscribed trace for different input frequencies can then be plotted. Phase response is more difficult to measure as the output of a recording system, a line on paper, is of different physical form from the input signal, an electrical voltage. In ambulatory recordings the time separation and the difference in the speed of the tape between recording and replaying further complicate the measurement of phase response.

To overcome these problems phase was measured using the technique described by Wagner.² The input signal was formed from a sine wave and its third harmonic. If the system under test had a linear phase response both frequencies would be delayed by the same amount and the output would not be distorted. If there was phase non-linearity distortion would occur. Measurement of the resulting distortion indicated the phase response of the device.³

Results for the machines that we assessed are shown in the Table, and responses for the ambulatory monitors appear in Fig. 3. The peak in amplitude response at 0.3–0.5 Hz by the recorders that used the

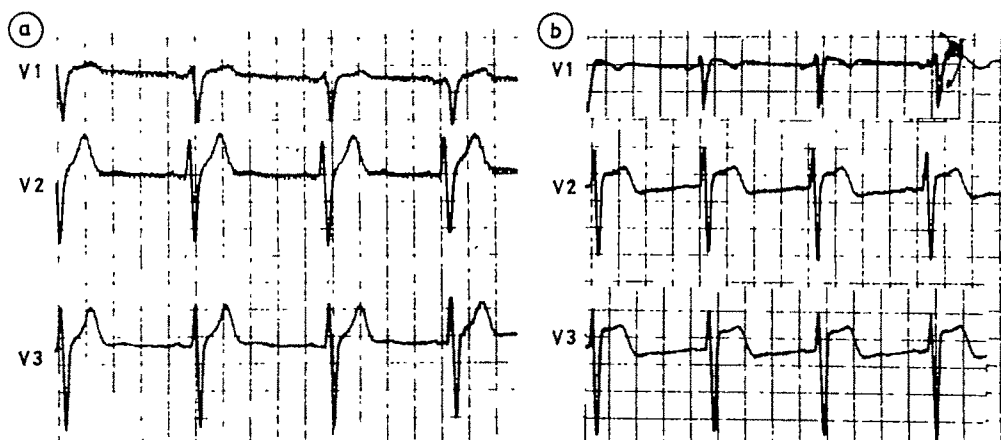


Fig. 2 (a) An electrocardiographic signal recorded without phase delay, and (b) the same signal with phase distortion but with amplitude response unchanged.

Table Characteristics of electrocardiographs tested

	Claimed to meet AHA's specification	Measured amplitude response	Phase response*	Electrocardiogram distortion	Baseline stability
Electrocardiographs:					
VS4 (Cambridge)	Yes	To AHA's specification	Satisfactory	None	Poor
Mingograf Minor (Siemens Elema)	Yes	To AHA's specification	Satisfactory	None	Poor
Ambulatory recorders:					
Medilog I/PB1 (Oxford Instruments)	No	Peak at 0.4 Hz, rapid low frequency fall off	Poor	Pronounced	Satisfactory
Medilog II/PB4 (Oxford Instruments)	Yes	To AHA's specification at low frequencies	Satisfactory	Loss of R wave	Fair (wave and noise)
Tracker/RP II (Reynolds Medical Electronics)	Yes	Peak at 0.3 Hz, rapid fall off (see Fig. 3)	Satisfactory (see Fig. 3b)	Some R wave attenuation	Poor
Monitor/Defibrillator:					
DMS 600 (Simonsen and Weel)	No	30% down at 0.5 Hz	Poor	Pronounced	Satisfactory
Monitor:					
Meddars Diagnostic	Yes	To AHA's specification	Satisfactory	None	Poor

*Phase response was satisfactory if the non-linearity was less than 6° over the physiological range of frequencies or poor if the non-linearity produced appreciable distortion of the electrocardiogram.
AHA, American Heart Association

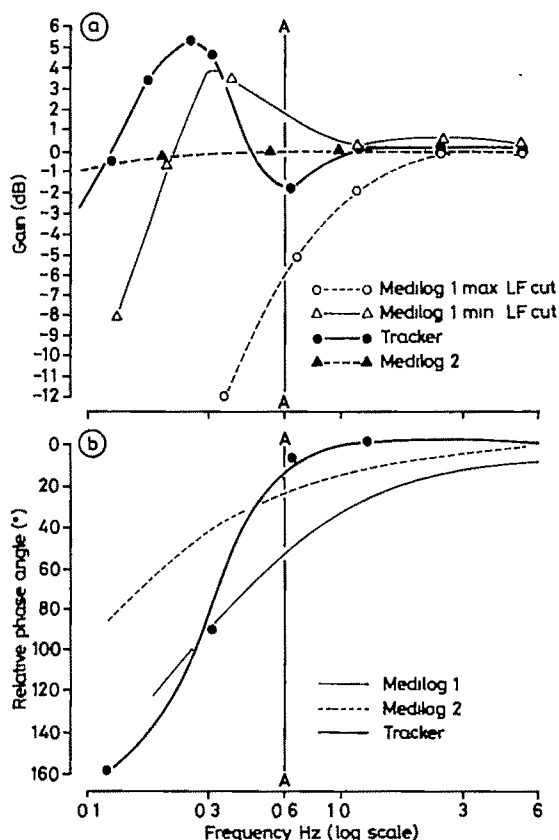


Fig. 3 (a) Amplitude response and (b) relative phase response for three ambulatory recorders. LF, low frequency.

direct recording method (Tracker and Medilog 1) was due to mechanical design of the tape replay heads and increased recorded noise, such as respiratory artefact, at this frequency. This occurred despite one manufacturer claiming that his machine met the American Heart Association's specification.⁴ The recorder amplifiers may have met this specification, but the overall record replay system did not. The amplitude response of the electrocardiographs and the Medilog II/PB4 recorder system met the American Heart Association's specification, though some examples of the Medilog II produced excessive electrical noise, which made ST segment shifts difficult to measure. Phase distortion began to occur with all machines at frequencies within the physiological range, above A-A (Fig. 3(b)), but was most noticeable with the Medilog I and the DMS 600.

MODIFICATION OF RECORDERS TO REDUCE DISTORTION (METHOD 4)

The distortion produced by the Medilog I/PB1 system was reduced by modifying its phase response. This was achieved in two ways. Firstly, a phase compensating network was inserted after the replay amplifier. This reduced distortion (Fig. 4) but increased low frequency amplification and so impaired baseline stability. Secondly, the tape was replayed backwards. Low frequency components that had suffered delays in recording were similarly delayed in the opposite direction on replay thus noticeably reducing phase distortion.⁵ The amplitude response was unchanged by this procedure, which resulted in a great improvement in recording quality (Fig. 4) but made timing of events difficult.

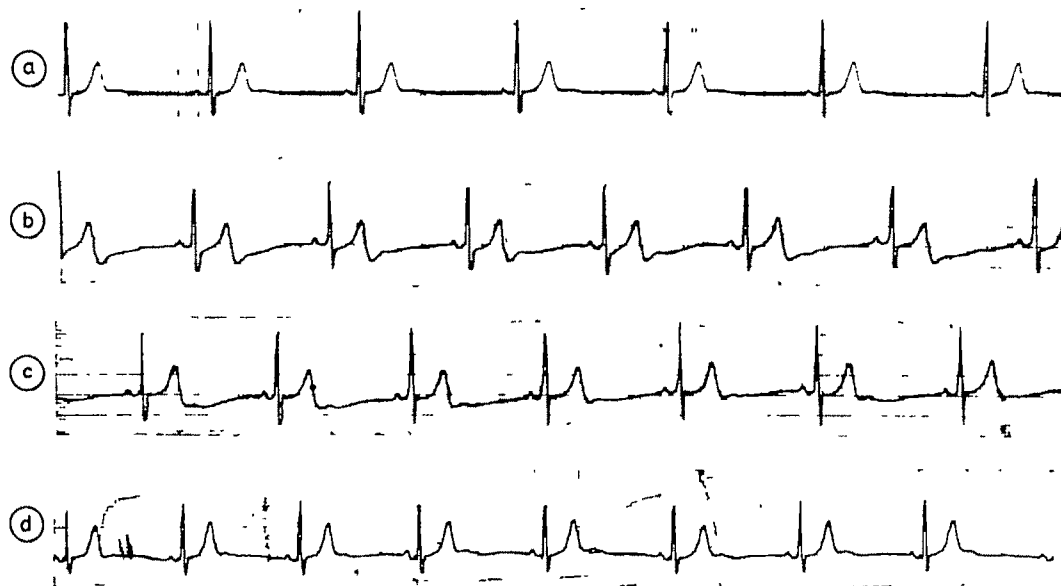


Fig. 4 Effect of phase distortion on electrocardiograms (a) recorded on a high quality electrocardiograph, (b) with the same signal recorded on a Medilog 1, (c) recorded on a Medilog 1 with phase correction, and (d) recorded on a Medilog 1 with the tape replayed backwards and inverted. Replaying the tape backwards had no effect on amplitude response but improved the phase response. (Copyright © 1983 IEEE.)

The phase response of the DMS 600 monitor was also improved by circuit changes made by the manufacturers. These changes reduced distortion but impaired low frequency stability by allowing the amplification of unwanted noise.

Case reports

The DMS 600 defibrillator/monitor analysed above has been carried by resuscitation ambulances in the Brighton area since 1973. Although primarily a high performance arrhythmia monitor, it is capable of recording a full 12 lead electrocardiogram. (A diagnostic trace recorded before admission to hospital can show important changes that are absent on later records.) We have, however, observed several instances of artefactual ST segment elevation or depression in electrocardiograms recorded by this machine. These artefacts simulated changes seen in disease states, led to additional investigations, and made diagnosis difficult. We present six cases in which distortion produced by such a machine impeded diagnosis.

CASE 1

A 33 year old man presented with central chest pain lasting for 45 minutes. Results of electrocardiography

performed in the ambulance showed anterior ST segment elevation. Repeat electrocardiograms in hospital were normal apart from minor lateral T wave changes, and there was no increase in cardiac enzyme activity. A week later he developed a second attack of pain, again with anterior ST segment elevation shown on the electrocardiograms recorded in the ambulance. Diagnostic quality traces were unchanged (Fig. 5(a)). An exercise stress test was normal with good exercise tolerance and satisfactory blood pressure response and his lateral T waves had returned to normal. A technetium scan and subsequent coronary angiography were also normal.

Having failed to find any abnormality in the patient we examined the electrocardiograph in the ambulance as described above. In addition, we noted that a computer generated electrocardiogram with isoelectric ST segments suffered distortion when recorded by the unmodified DMS 600. In a further experiment the electrocardiogram of this patient was reconstructed by digitising his hospital recordings and using a MINC computer (Digital Equipment Corporation) to recreate the electrical waveform. The recreated signal was recorded simultaneously by a VS4 electrocardiograph and the DMS 600. Artefactual ST segment changes are clearly visible (Fig. 6).

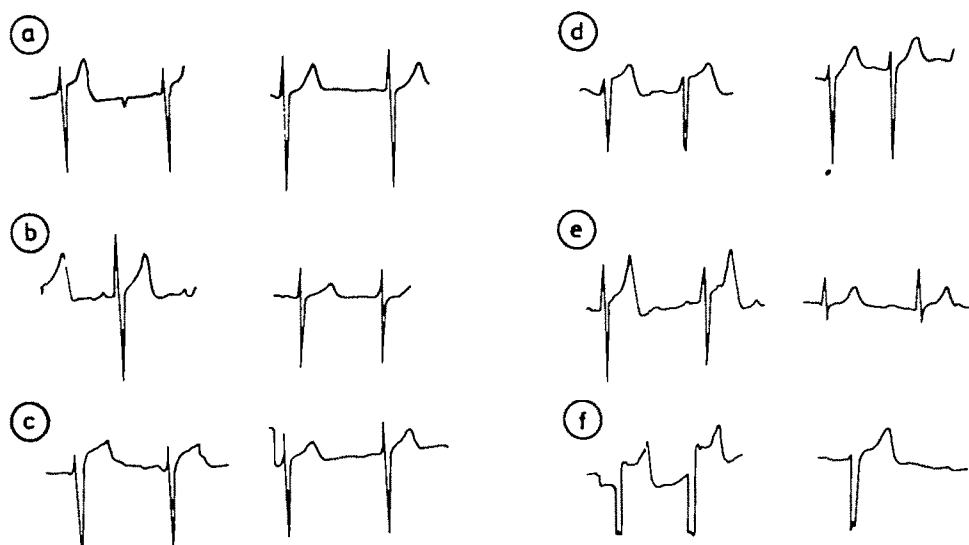


Fig. 5 Anterior complexes recorded from cases 1-6 labelled (a) to (f) respectively. The electrocardiogram recorded in the ambulance is shown on the left, recordings of diagnostic quality on the right.

CASE 2

A 73 year old woman had suffered from exertional angina for 10 years and hypertension with dizzy spells for one year. On admission her chest pain was relieved by treatment with glyceryl trinitrate; she then col-

lapsed. The electrocardiogram taken in the ambulance showed ST segment elevation in leads V2 and V3 and ST segment depression in the lateral chest leads (Fig. 5(b)). A repeat trace one hour later by a diagnostic quality electrocardiograph was normal apart from left axis deviation and plane ST segments in V5 and V6. Physical examination was normal except for mild hypertension. No increase in cardiac enzyme activity was seen. An erroneous diagnosis of Prinzmetal's angina was made initially in this patient.

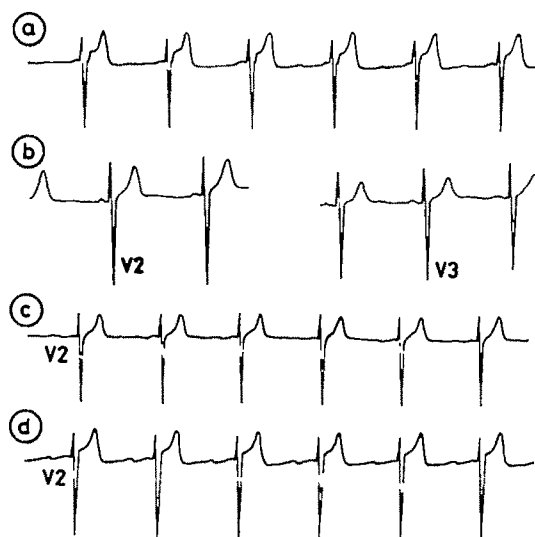


Fig. 6 Electrocardiograms recorded (a) in the ambulance, (b) in casualty, (c) reformed and recorded on VS4, and (d) reformed and re-recorded on the ambulance machine showing ST segment distortion produced by the DMS 600 electrocardiograph. (c) and (d) are simultaneous recordings of the same signal performed on different machines.

CASE 3

A 35 year old man developed a sudden attack of chest pain while sitting an important examination. The pain radiated to his throat and was associated with paraesthesiae in his left arm. There was no relevant medical or family history. Physical examination was normal. The electrocardiogram taken in the ambulance showed ST segment elevation in the anterior leads, but subsequent inpatient electrocardiograms were all normal (Fig. 5(c)). An exercise stress test was normal, and a gated technetium scan showed normal wall motion with an ejection fraction of 53%.

CASE 4

A 34 year old man developed pain over his left chest radiating to his left arm while lifting a heavy girder. He drank three quarters of a bottle of gin with no relief. On examination he had a tender chest wall, and the pain was reproduced by external rotation of his arm. The electrocardiogram taken in the ambulance showed ST segment elevation in the anterior leads

with lateral ST segment depression. The trace taken in the accident and emergency department was normal (Fig. 5(d)).

CASE 5

A 73 year old man with hypertension had a 12 hour history of episodes of pain relieved by treatment with glyceryl trinitrate. Physical examination was normal apart from mild hypertension (160/80 mm Hg). The electrocardiogram recorded in the ambulance showed ST segment elevation in the anterior leads (Fig. 5(e)). The trace recorded in the accident and emergency department showed inferior ischaemia only. Cardiac enzyme activity and results of other routine biochemical tests were normal, and an exercise stress test showed further inferior ischaemia with no anterior changes.

CASE 6

A 65 year old man was diagnosed as having aortic valve disease in 1979. As his angina and dyspnoea worsened he was entered on a waiting list for cardiac catheterisation. On admission he had experienced severe chest pain, which had not been relieved by treatment with sublingual nitrates. An electrocardiogram recorded in the ambulance showed ST segment elevation; the trace recorded in the accident and emergency department was normal. We immediately repeated the recording using the machine in the ambulance and again produced artefactual ST segment elevation (Fig. 5(f)). Cardiac enzyme activity failed to show a diagnostic increase.

Discussion

It is important that diagnostic equipment should give reliable information with minimal chance of error. There should be no need to question whether the information is an artefact or real. It is also important both that the performance of equipment is defined and that manufacturers' claims of function and accuracy are validated.

We investigated the effect of a non-linear phase response on the electrocardiogram both theoretically, with computer modelling and an all pass filter, and in practice, with ambulatory recorders and a monitor defibrillator. We showed that phase distortion may cause electrocardiographic changes similar to those seen in disease states and that this may cause difficulties in diagnosis. Only by repeating recording signals, as in cases 1 and 6, could we prove that the electrocardiographic changes seen in the six cases were not due to transient myocardial ischaemia; but the observations in all are persuasive.

The effect of filtering on the electrocardiogram was investigated by Pipberger *et al*, Berson and Pip-

berger, and Meyer,⁶⁻⁸ and this work led to the current American Heart Association's recommendation for electrocardiographs.⁹ They used simple analogue filters and did not attempt to separate amplitude and phase effects. Current standards specify that the gain of the machine should be substantially constant down to 0.14 Hz, should be not less than 30% of the mid-frequency gain at 0.05 Hz, and should fall only slowly at lower frequencies. Unfortunately, these recommendations make no mention of phase response, and, as we have shown, it is possible to build circuitry that will meet these specifications but will still produce gross distortion of the electrocardiogram.

The extended amplitude response at low frequencies suggested by the American Heart Association does not allow effective attenuation of low frequency noise such as respiratory artefact. This causes difficulty when monitoring active subjects or in electrically noisy situations such as the catheter laboratory. As the electrocardiogram is repetitive it should contain no frequencies lower than the reciprocal of the RR interval. Several authors support this view,¹⁰⁻¹² and Hyndman produced experimental evidence to suggest that there are no components in a normal electrocardiogram with frequencies lower than 0.5 Hz.¹³ Our results using the all pass filter confirm this opinion.

Simple analogue filters produce phase distortion at frequencies up to 10 times greater than those at which significant amplitude attenuation occurs. The American Heart Association therefore specifies a frequency of 0.05 Hz for the 30% amplitude attenuation point in an attempt to ensure minimal phase distortion at 0.5 Hz and above. Equipment contains more than simple filters, however, and it is naive to suggest that by specifying such an amplitude characteristic the phase response will necessarily be linear over the physiological range. Indeed the all pass filter will have no effect on the amplitude response but may produce gross distortion of electrocardiographic signals. Phase distortion is particularly serious as it causes changes resembling ischaemia. Moreover, these changes may not always be present as they depend on the morphology of the displayed electrocardiogram.

Ambulatory recorders were developed initially for arrhythmia monitoring and only later used for ST segment analysis. In arrhythmia monitoring P waves and QRS complexes are of prime consideration, and T wave fidelity may be sacrificed to achieve a stable baseline in ambulatory subjects. Several of the recorders have been criticised when used to monitor ST segments,¹⁴ and Bragg-Remschel *et al* reviewed several different types showing many with pronounced phase non-linearity and peaks in their amplitude responses.¹⁵

The electrocardiograph that distorted the traces of

our patients had an amplitude response that had decreased by 30% at 0.5 Hz. This decrease on its own would have caused less than 0.02 mV distortion of the ST segment, but the phase response was noticeably non-linear at frequencies contained within patients' electrocardiograms. It was therefore phase effects that caused the distortion rather than a poor amplitude response.

In analogue filters phase and amplitude responses are often linked but digital filters using microprocessor techniques can be designed with both a linear phase response and amplitude characteristics that provide superior noise reduction.^{16,17}

We propose that an ideal electrocardiograph should have the following characteristics: (a) flat amplitude response from 0.5 Hz to 75 Hz (to cover the physiological range of frequencies); (b) no response below this frequency to minimise noise; and (c) linear phase response from 0.5 Hz to 75 Hz. This ideal is impossible to realise at present, but the specifications for electrocardiographs, including the International Electrotechnical Commission draft specification,¹⁸ should be changed in order to encourage future developments. Several electrocardiographs do incorporate digital filtering and at least two of them claim to have a phase response that is linear.

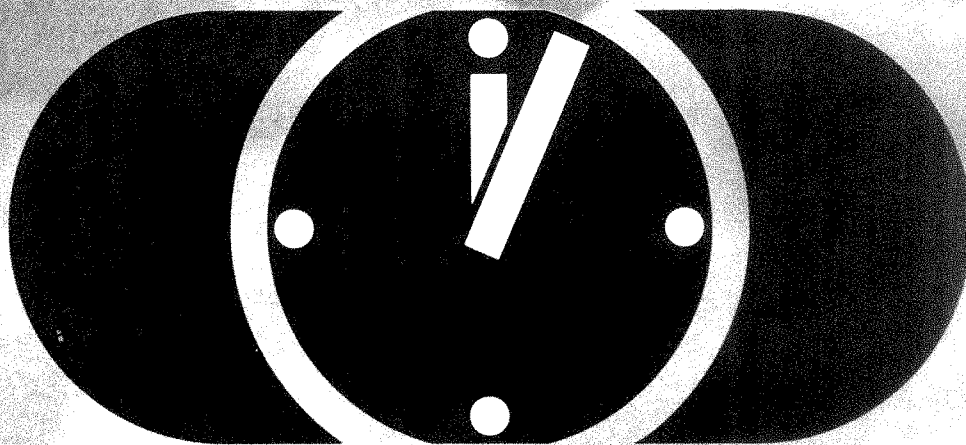
An extended amplitude response should not be relied upon in an attempt to ensure phase linearity over the physiological range. A more limited amplitude response improves baseline stability and need not increase distortion provided the phase response is satisfactory. We have insufficient data to recommend guidelines for the magnitude of the variation allowed from the ideal linear phase response. Nevertheless, both phase and amplitude responses of a recorder should be specified as the phase response of an electrocardiograph is as important, if not more so, than its amplitude response.

We thank patients and staff at the Royal Sussex County Hospital, Brighton, for their cooperation, and Dr D A Chamberlain, Dr D J Woollons, and Dr M J English for their helpful advice. DIT received support from the British Heart Foundation as junior research fellow for much of this study. Fig. 4 is reproduced by kind permission of the Institute of Electrical and Electronics Engineers, Inc.

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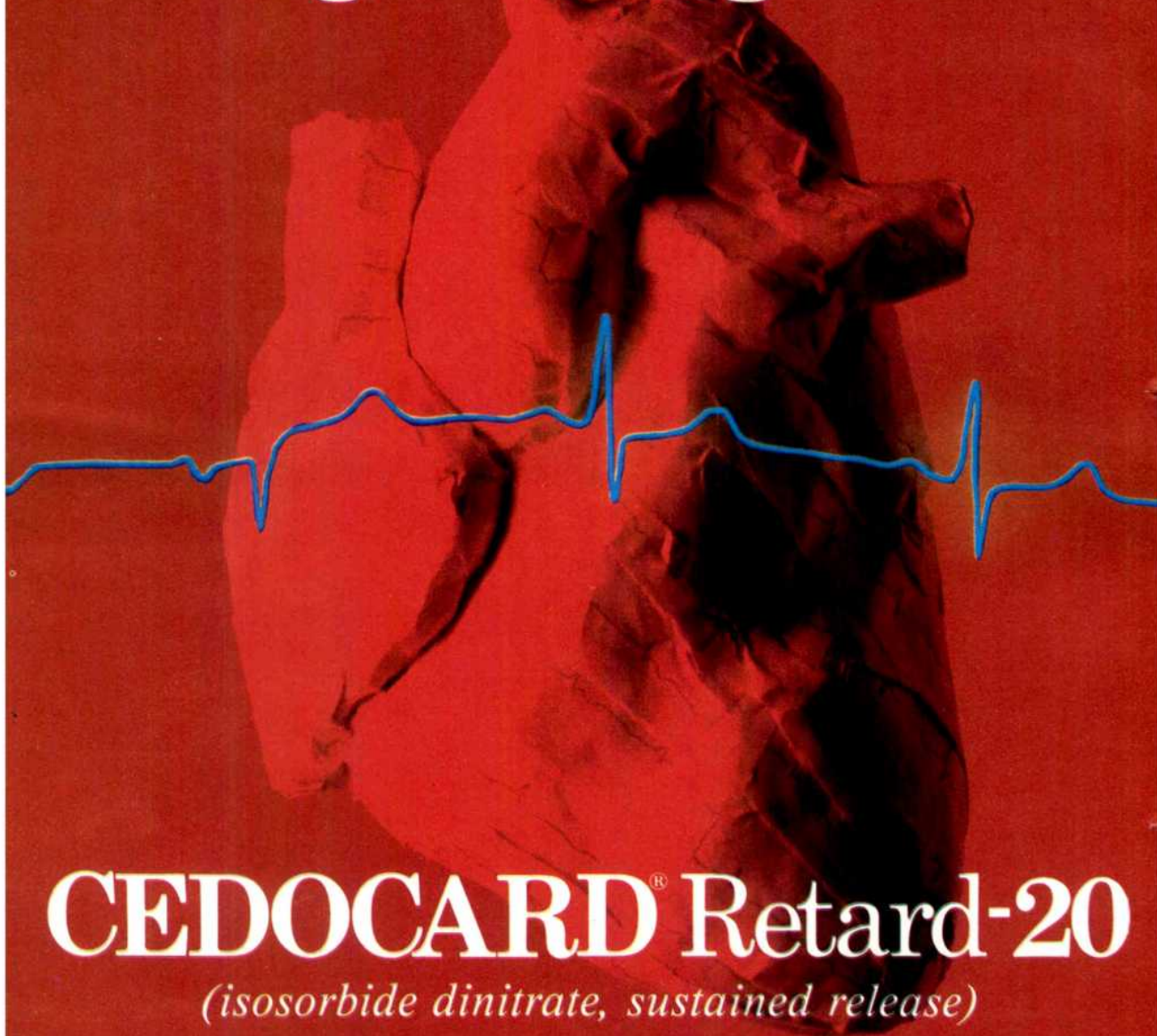


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Acute coronary occlusion during percutaneous transluminal coronary angioplasty

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From the *Queen Elizabeth Hospital, Birmingham; †Leeds General Infirmary, Leeds; and the ‡Northern General Hospital, Sheffield

SUMMARY Two hundred and forty percutaneous transluminal coronary angioplasty procedures were performed in three centres over a two year period. Acute occlusion of the vessel undergoing angioplasty was seen on 20 (8%) occasions. The cause of occlusion was determined angiographically and in some cases confirmed at the time of emergency open heart surgery. The mechanism of coronary occlusion was arterial dissection in six cases, persisting coronary arterial spasm in seven, and coronary thrombosis in four. In three patients the mechanism could not be determined. Immediate reintroduction of a balloon dilatation catheter was attempted in 10 patients and resulted in restoration of adequate coronary flow in six. The remaining 14 patients underwent open heart surgery as an emergency procedure.

Percutaneous transluminal coronary angioplasty is now an accepted treatment for patients with angina and technically suitable coronary artery lesions. A major acute complication is coronary occlusion. Although this may be treated medically, emergency bypass grafting is often performed in the hope of myocardial salvage. In order to reduce the incidence of acute occlusion during percutaneous transluminal coronary angioplasty and rationalise its management, this review was undertaken to identify the mechanisms responsible for this complication.

Patients and methods

The first 240 percutaneous transluminal coronary angioplasty procedures in the three cardiothoracic centres were reviewed to determine the incidence of acute coronary occlusion. There were 209 patients (171 male and 38 female, a sex ratio of 4.5 to 1), whose ages ranged from 29 to 69 (mean 50) years. Table 1 shows the distribution of coronary arteries affected and the overall success and complications. All except five patients underwent angioplasty of one coronary artery per procedure.

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Accepted for publication 9 April 1985

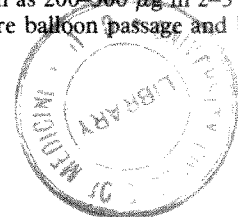
Table 1 Distribution of coronary arteries affected and outcome. Figures are numbers (%)

	All procedures	Acute occlusions
No of procedures	240	20
No of patients	209	20
Male/female (ratio)	171/38 (4.5:1)	11/9
Age range (years)	29-69 (mean 50)	38-63 (mean 50)
Target vessels:		
LAD	147	12
RCA	64	7
Cx	13	1
Vein grafts	10	—
Primary success	182 (76)	—
Emergency CABG	16 (6.6)	13
Death	3 (1.3)	2

LAD, left anterior descending artery; RCA, right coronary artery; Cx, circumflex artery; CABG, coronary artery bypass graft.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Percutaneous transluminal coronary angioplasty was performed from the femoral route using a standard technique.^{1,2} Steerable balloon catheters with a freely movable guide wire were used in 128 of the 240 cases. All procedures were performed in the cardiac catheterisation laboratory under local anaesthesia. Before angioplasty patients received three days' treatment with aspirin 300 mg daily, dipyridamole 100 mg three times daily, nifedipine 10 mg three times daily, and long acting nitrates. Intracoronary glyceryl trinitrate was given as 200-300 µg in 2-3 ml of saline immediately before balloon passage and be-



tween periods of balloon inflation as appropriate. In addition, nitrate was given during the procedure sublingually by transdermal patches or as an intravenous bolus of 5 mg isosorbide dinitrate at the start of the procedure. The precise dosage and route were dictated by patient tolerance. Anticoagulation during the procedure was with heparin 10 000 units intravenously at the start of the procedure with a further 5000 units after one hour if necessary.

ANGIOGRAPHIC ANALYSIS

Acute occlusion of the target vessel was defined angiographically as a total lack of contrast opacification beyond the point of occlusion or absolute stasis of coronary flow where some distal opacification was present. None of the cases under consideration had total occlusion before the procedure. In every instance the acute occlusion that followed the procedure was recognised before the patient was returned to the ward. Angiograms were reviewed retrospectively and the mechanism of occlusion decided by consensus using the following guidelines.

Coronary dissection—Patients with limited areas of coronary dissection related to balloon angioplasty not resulting in interference with coronary flow were excluded. Occlusion from dissection was recognised by multiple views of the obstructed vessel showing the presence of an extensive area of intimal elevation, extravasation of contrast medium, or persistent staining of the vessel wall (Figs. 1 and 2). The diagnosis of arterial dissection was generally confirmed at the time of emergency bypass grafting.

Coronary spasm—A tapering appearance of the site of occlusion in the absence of the above features suggestive of dissection was taken as probably due to coronary spasm (Fig. 3). Additional helpful features were partial and transient response to intracoronary nitrate injections. Only patients with occlusion despite repeated intracoronary nitrate administration were included in this study. In these cases no specific features were noted at the time of emergency surgery.

Coronary thrombosis—Intracoronary thrombus formation leading to occlusion was diagnosed by the presence of persistent intravascular filling defects associated with coronary stasis. Distal branches may be faintly opacified with central filling defects, giving a ghosting appearance. All cases categorised as being due to thrombosis were confirmed at emergency operation by the finding of thrombotic material in the vessel.

Others—Three cases of acute occlusion showed none of the above angiographic features.

Results

Acute coronary occlusion was found in 20 patients

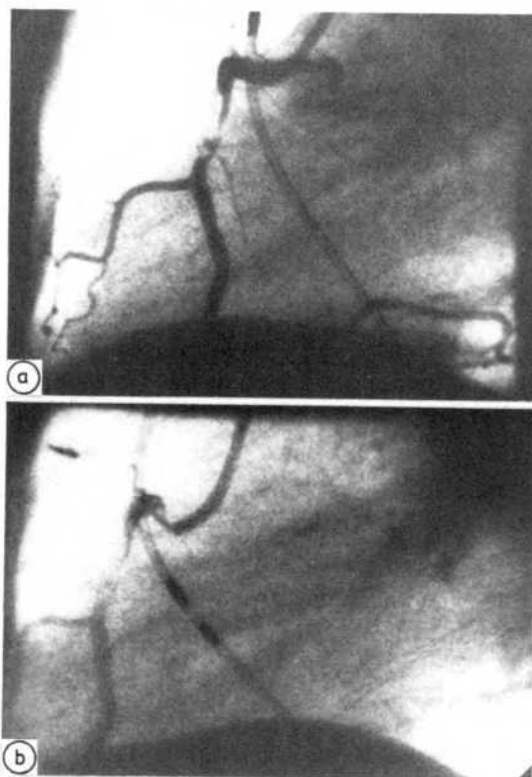


Fig 1 Angiograms showing acute coronary occlusion secondary to dissection in a man aged 48 (case 1). (a) Shows a limited dissection initially adjacent to the site of stenosis. Minutes later the dissection caused cessation of antegrade flow with only faint opacification of the distal lumen (b). A repeat procedure was unsuccessful.

(nine women, 11 men) out of a total of 240 (8.3%) procedures. Their mean age was 50 years, the age distribution being similar to that of the whole series of patients undergoing percutaneous transluminal coronary angioplasty. The distribution of affected arteries was left anterior descending 12, right coronary artery seven, and circumflex artery one, which was also not different from that present in the whole group (Table 1). Acute occlusion accounted for 14 of all 16 emergency bypass graft operations and two of the three deaths.

MECHANISM OF OCCLUSION

The cause of acute occlusion was judged angiographically to be due to dissection in six cases, spasm in seven, and thrombosis in four. No specific angiographic features were found in three patients. Table 2 shows clinical features and outcome of the four groups of patients. Coronary artery bypass grafting was required for all four patients in whom occlusion was

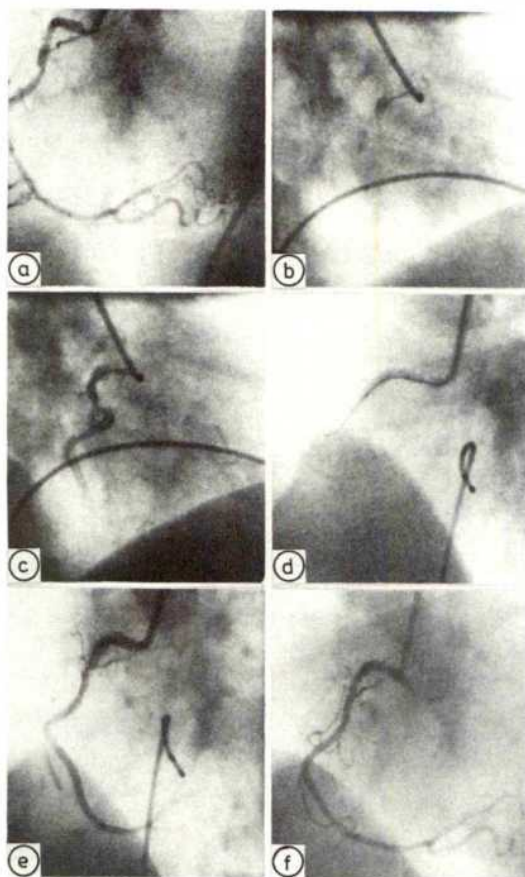


Fig 2 Angiograms showing acute coronary occlusion secondary to dissection in a woman aged 52 (case 4). (a) Shows a mid right coronary artery stenosis. During attempted passage of the balloon catheter contrast staining of the vessel wall was seen (b), and contrast injection showed occlusion with no effective antegrade flow (c). After a repeat procedure (d) antegrade flow was re-established (e), and a follow up angiogram at seven months showed no residual disease (f).

due to thrombosis, in three in whom no definite angiographic features were seen, in four cases of dissection, and in three cases of coronary spasm. Of the two deaths, one occurred in a patient with dissection and one in a patient with spasm, but in the last instance the spasm was complicated further by the formation of thrombus distal to the site of spasm. Non-fatal myocardial infarction occurred in five patients (25% of those with occlusion). In only four (20%) patients was clinical progress entirely uncomplicated after acute occlusion with neither myocardial infarct nor emergency bypass graft. Three had severe spasm and one had coronary dissection. All four had a

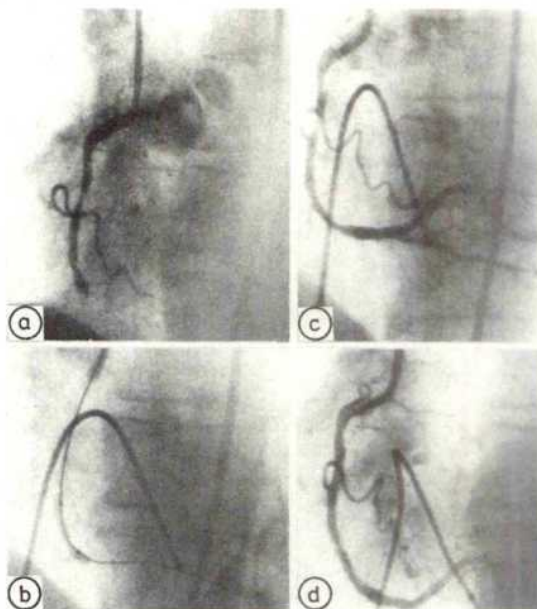


Fig 3 Angiograms showing acute occlusion caused by coronary spasm in a woman aged 58 (case 11). After angioplasty of two sequential right coronary artery stenoses distal occlusion occurred with a tapering appearance suggestive of spasm (a). Response to nitrate treatment was inadequate, and a repeat procedure was performed (b). An immediate (c) and repeat angiogram at one week (d) showed a patent vessel.

successful immediate repeat angioplasty for acute occlusion.

STEERABLE AND NON-STEERABLE SYSTEMS

There was no apparent difference in the incidence of coronary occlusion whether steerable or non-steerable balloon catheters were used. Steerable systems were used in 54% of all patients undergoing the procedure (Table 1) and in 11 of the 20 (55%) cases of acute occlusion. Successful recanalisation after occlusion was more likely with steerable systems, being successful in five out of seven attempts. Only one of the three attempts at recanalisation with the non-steerable system was successful.

REPEAT ANGIOPLASTY

A repeat procedure was attempted in three patients with dissection and was completely successful in one. In another patient (case 3, Table 2) apparent angiographic recanalisation was followed by death after 12 hours. From the postmortem findings it was thought likely that the false rather than the true lumen of the vessel was recanalised to provide a communication with the distal vessel. A repeat procedure was performed in five of the six cases of coronary spasm and

Table 2 Outcome of patients with occlusion due to coronary dissection, coronary spasm, and coronary thrombosis, and miscellaneous causes

Case No	Age/sex	Vessel	Catheter	Repeat angioplasty	CABG	Outcome/comments
<i>Coronary dissection</i>						
1	48/M	RCA	N-S	Failed	Yes	No MI, home
2	49/F	LAD	S	NA	Yes	No MI, home
3	47/M	LAD	S	Apparent success	No	Died at 12 hours, necropsy showed extensive dissection
4	52/F	RCA	S	Success	No	No MI, home; follow up at 7 months showed normal RCA
5	55/F	LAD	N-S	NA	Yes	No MI, home
6	63/M	LAD	S	NA	Yes	Perioperative MI, home
<i>Coronary spasm</i>						
7	56/M	LAD	N-S	Successful	No	No MI, follow up angiogram normal at 6 months
8	38/M	LAD	N-S	NA	Yes	No MI, home
9	39/M	RCA	S	Successful	No	No MI, home
10	53/M	LAD	S	Successful	No	Clinical MI, home
11	58/M	RCA	S	Successful	No	No MI, follow up angiogram at one week showed patent vessel
12	57/F	RCA	N-S	Failed	Yes	Thrombus distal to spasm site, died 12 hours after CABG
13	44/M	RCA	S	Failed	Yes	No MI, home
<i>Coronary thrombosis</i>						
14	62/M	LAD	N-S	NA	Yes	MI, home
15	41/F	LAD	S	Failed	Yes	MI, home
16	45/F	RCA	N-S	NA	Yes	No MI, home
17	56/F	LAD	N-S	NA	Yes	No MI, home
<i>Miscellaneous causes</i>						
18	56/M	LCx	N-S	NA	Yes	No MI, balloon inflated proximal to stenosis
19	49/M	LAD	S	NA	Yes	MI, balloon inflated in side branch
20	36/M	LAD	S	NA	Yes	No MI, no obvious cause of occlusion

N-S, non-steerable; S, steerable (balloon catheter system); CABG, coronary artery bypass grafting (emergency); NA, not attempted; MI, myocardial infarct; LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex.

was successful in four. Although one patient had myocardial infarction, none of the four required bypass grafting. Follow up for a mean of seven months after angioplasty showed good clinical results (Table 2). Of the two failed repeated procedures in this category, in one patient (case 12, Table 2) there was angiographic evidence of distal thrombosis formation secondary to unrelieved spasm despite repeated balloon dilatation and maximal treatment with nitrate and a calcium antagonist. This patient died despite emergency bypass grafting.

Repeat angioplasty was attempted in one case of coronary occlusion due to thrombus formation and was unsuccessful. All four patients with thrombotic occlusion and the three with non-specific occlusion underwent bypass grafting, and in these two sub-groups there were no hospital deaths. In two patients review of the angiograms suggested that the cause of the occlusion was malposition of the balloon at the time of inflation, either proximal to the lesion or in an immediate side branch.

Discussion

Acute coronary occlusion at the time of percutaneous

transluminal coronary angioplasty often leads to further serious complications.³⁻⁵ In the National Heart, Blood and Lung Institute series reported by Cowley *et al* coronary occlusion accounted for 64% of myocardial infarcts, 93% of emergency bypass operations, and 63% of inpatient deaths.⁵ Of the 20 cases reported here, 14 required emergency surgery, five sustained clinical myocardial infarctions, and two died. Only four (20%) patients had coronary occlusions resolved without any major complications or surgery.

Simple occlusion without a definitive diagnosis of spasm or dissection occurred between 4% and 5% in the series reported by Kent *et al*³ and Dorros *et al*.⁴ When occlusion due to any cause is included, the incidence is between 9% and 12% for these large series of cases. We defined occlusion complicating percutaneous transluminal coronary angioplasty as either the complete absence of vessel opacification by contrast injection or a lack of antegrade flow in an opacified vessel. Our incidence of 8.3% is comparable to that in previous reports.

Female patients were at higher risk from occlusion, occurring in nine out of 39 (23%) instances, whereas the risk in male patients was only 6.4%. Four out of

six cases of occlusion from vessel dissection affected female patients. Age and the vessel involved did not appear to be a relevant factor. This observation again supports previous experience that the overall risk of percutaneous coronary angioplasty is higher in women.⁴

In our experience it is often difficult to establish the actual cause of acute occlusion at the time of the complication, and some of the cases were classified retrospectively with the help of full screen projection of the cineangiograms. We have found the need for several projection angles to identify features such as intimal elevation in dissection and filling defects in thrombotic occlusion. From our limited experience, angiographic diagnosis of the mechanism of occlusion seems to be helpful in the immediate management of the patient.

Emergency bypass surgery was necessary in all our cases of thrombotic occlusion. Although the use of streptokinase may prove useful, so far it has been used only to gain time to prepare for emergency surgery.⁶ Some of our cases were due to prolonged procedures and too little anticoagulation. With rigid adherence to the recommended doses⁷ and shorter procedure time with increased operator experience this complication may be reduced.

Our experience of successful immediate repeat angioplasty in four out of six attempts in dealing with occlusion due to spasm accords with Hollman *et al*'s report that emergency bypass surgery can often be avoided this way.⁷ The role of repeat angioplasty in occlusion due to dissection is less well established. Repeat balloon inflation may maintain antegrade flow by pushing back the loose intimal flap. A major hazard in this approach is canalisation of the false passage resulting in worsening of the dissection. The steerable system does allow less traumatic exploration of the vessel with soft tipped wires than the balloon catheter and should be exclusively used for this purpose.

In conclusion, we found acute coronary occlusion of the target vessel to be the single most important cause of morbidity and mortality with percutaneous transluminal coronary angioplasty. Angiographic diagnosis of the actual mechanism of occlusion was useful as it has a bearing on the subsequent management. More experience is required to define the role of immediate repeat angioplasty, but it appears to be indicated in cases due to spasm. Strenuous efforts should be made towards the prevention of occlusion from any cause complicating coronary angioplasty.

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Effect of smoking habits and timolol treatment on mortality and reinfarction in patients surviving acute myocardial infarction

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SUMMARY The Norwegian Multicenter Group Study noted the effect of smoking habits before and after myocardial infarction and their relation to mortality and reinfarction rate after treatment with timolol in patients surviving acute myocardial infarction. The mean follow up period was 17.3 (range 12-33) months. No relation was found between initial smoking habits and risk category after infarction or between initial smoking habits and later outcome. At the time of their first infarct smokers were seven years younger than non-smokers. One month after infarction nearly 60% of the smokers had stopped smoking completely. A significantly lower incidence of early cardiac death and lower total mortality was found in patients treated with timolol in both those who continued smoking and in the combined non-smoking groups and a significantly lower reinfarction rate among non-smokers. Cessation of smoking alone was associated with a reduced reinfarction rate by 45% but a non-significant reduction in mortality by 26%.

It is concluded that treatment with timolol and cessation of smoking have an additive effect in reducing mortality and reinfarction rate after myocardial infarction.

The use of beta-receptor blockers after acute myocardial infarction has been found to reduce overall mortality.¹⁻³ The effect of smoking habits on mortality and reinfarction in these patients has, however, not been reported. In this report we present a detailed analysis of the Norwegian multicenter timolol trial¹ with respect to smoking habits before and after infarction and their correlation with prognosis.

Patients and methods

A detailed description of the study design, eligibility criteria, follow up procedures, end point evaluation, data handling, and statistical methods has been published.¹ Treatment with timolol 10 mg twice daily was started 7-28 days after the onset of symptoms. The patients were stratified to three risk groups: group 1 consisted of patients with recurrent myocardial infarction with or without conditions for possible high risk; group 2 consisted of patients with a first myocardial

infarction and one or more of five high risk conditions¹; and group 3 consisted of patients not at high risk (the remaining patients).

STUDY POPULATION

A total of 1884 patients were included in the study. Of these, 945 patients were randomised to treatment with timolol (752 men and 193 women), and 939 to treatment with placebo (732 men and 207 women). The patients were followed for 12-33 months (mean 17.3 months). Smokers were given individual advice on the relation of continued smoking and their heart disease and were encouraged to stop. Smoking habits were assessed by an interview at each visit.

Smoking data for the 12.2% of the patients with acute myocardial infarction who died before inclusion or for patients who were excluded from entry for other reasons were not recorded.

CLASSIFICATION

Patients were classified as non-smokers if they had never smoked, as ex-smokers if they had stopped smoking more than one month before the infarction, as new ex-smokers if they had stopped smoking after

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Accepted for publication 2 April 1985

Table 1 Initial smoking habits in patients surviving myocardial infarction according to risk group. Figures are numbers (%) of patients

	Group 1 (n=352)	Group 2 (n=1091)	Group 3 (n=441)	Groups combined (n=1884)
Smokers	151 (42.9)	613 (56.2)	241 (54.7)	1005 (53.3)
Ex-smokers	131 (37.2)	235 (21.5)	106 (24.0)	472 (25.1)
Non-smokers	70 (19.9)	243 (22.3)	94 (21.3)	407 (21.6)
Smokers (grams of tobacco smoked):				
1-4	29 (19.2)	50 (8.2)	27 (11.2)	106 (10.5)
5-14	83 (55.0)	359 (58.5)	142 (58.9)	584 (58.1)
15-24	27 (17.9)	147 (24.0)	60 (24.9)	234 (23.3)
>25	12 (7.9)	57 (9.3)	12 (5.0)	81 (8.1)
Duration of smoking (years)				
0-9	—	5 (0.8)	1 (0.4)	6 (0.6)
10-24	14 (9.3)	78 (12.7)	26 (10.8)	118 (11.7)
25-39	45 (29.8)	243 (39.7)	104 (43.2)	392 (39.0)
>40	92 (60.9)	287 (46.8)	110 (45.6)	489 (48.7)

the infarction for one month or more, and as smokers if they continued smoking. One cigarette was defined as 1 g of tobacco, one cigarillo as 2 g, and one cigar as 5 g.

OUTCOME

Early cardiac death was defined as death occurring without previous symptoms or within 24 hours of the onset of new symptoms of heart disease.

Results

SMOKING HABITS AND INFARCT CHARACTERISTICS

Table 1 shows the smoking habits in the three risk groups of the patients surviving the acute stage of the myocardial infarction. One thousand and five patients (53.3%) were smokers before the infarct (59.4% of men and 31% of women), 472 (25%) ex-smokers, and 407 (21.6%) non-smokers. Of the smokers, 849 (84.5%) smoked cigarettes, nine (0.9%) cigarillos or cigars, and 147 (14.6%) pipes. Of the smokers, 935 (93%) inhaled and 70 (7%) did not. The non-inhalers and pipe smokers were equally distributed among the risk groups, and because of the small number they are included in the smoker group in this analysis.

Several hundred comparisons of patient characteristics within and among risk groups were made. The differences between the treatment groups tended to be small, and when the differences are adjusted for by the Cox regression model they did not influence the life table analyses.

The total mortality in the placebo treated patients was highest in risk group 1 (17.8%) followed by risk group 2 (13.6%), and lowest in risk group 3 (5.4%).

The distribution of smokers, ex-smokers, and non-smokers was similar in risk groups 2 and 3, as was the amount of tobacco smoked and the duration of smoking. Of the smokers, 59% smoked 5-14 g of

tobacco daily, and 9.3% in risk group 2 and 5.0% in risk group 3 (not significant) smoked >25 g. Mean duration for smoking was 35.4 years (37.2 years for men and 27.4 years for women). Very few patients had smoked for less than 10 years (12 patients).

In risk group 1 (recurrent infarction) there were significantly fewer smokers ($p<0.01$) and significantly more ex-smokers ($p<0.001$) than in the other risk groups. Smokers with a recurrent infarction had a lower tobacco consumption than smokers with a first myocardial infarction. Of the smokers in risk group 2, 8.2% had a low tobacco consumption of 1-4 g daily compared with 19.2% of smokers with a recurrent infarction ($p<0.001$). Twenty four per cent of smokers in risk group 2 compared with 17.9% in risk group 1 ($p<0.001$) smoked 15-24 g daily. The ex-smokers (risk groups combined) had stopped smoking for a mean of 11.1 years before inclusion in the study and had been smoking for a mean of 28.4 years before they stopped.

Smoking habits in patients surviving the acute phase of a first myocardial infarction therefore seem not to be correlated with high or low risk categories after myocardial infarction. Nevertheless, subjects with recurrent infarction have a lower tobacco consumption than those with a first myocardial infarction. Likewise we found no correlation between smoking habits at the time of infarction and later death.

Age at inclusion in the study was correlated with smoking status. Smokers who survived their first complicated infarct (risk group 2) were 6.8 years younger than non-smokers (58.4 years vs 65.2 years) and four years younger than ex-smokers.

INITIAL SMOKING HABITS AND OUTCOME

Table 2 shows the distribution, according to initial smoking habit, of the number of all deaths, early cardiac deaths, and non-fatal reinfarctions occurring dur-

Table 2 Frequency distribution of deaths and reinfarctions by initial smoking status in patients treated with placebo (P) or timolol (T). Figures are numbers (%) of patients

Category	Smoker		Ex-smoker		Non-smoker		All combined	
	P	T	P	T	P	T	P	T
Total No of patients	493	512	234	238	212	195	939	945
Deaths during treatment or within 28 days of withdrawal:								
Early cardiac death	50 (10.1)	28 (5.5)*	24 (10.7)	9 (3.8)**	20 (9.4)	10 (5.1)	95 (10.1)	47 (5.0)***
All deaths	58 (11.8)	37 (7.2)*	34 (14.5)	13 (5.5)**	25 (11.8)	17 (8.7)	117 (12.5)	67 (7.1)***
Non-fatal reinfarctions during treatment or within 28 days of withdrawal	58 (11.8)	48 (9.4)	38 (16.2)	19 (8.0)**	29 (13.7)	13 (6.7)*	141 (15.0)	88 (9.3)***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

ing treatment or within 28 days of withdrawal from the study. The total number of deaths were 117 in the placebo group and 67 in the timolol group ($p < 0.001$), a reduction of 43%. The number of early cardiac deaths was 95 in the placebo group and 47 in the timolol group ($p < 0.001$). Overall mortality and the incidence of early cardiac death were significantly reduced in the ex-smokers ($p < 0.01$) and initial smokers ($p < 0.05$) treated with timolol. The reduction in the number of early cardiac deaths and of all deaths in the non-smoker group was not significant. We found no difference in the incidence of early death, all deaths, or reinfarction between timolol treated smokers and timolol treated ex-smokers or between placebo-treated smokers and placebo-treated ex-smokers.

The number of initial reinfarctions was 141 in the placebo group and 88 in the timolol group ($p < 0.001$), a reduction of 38%. The incidence of initial reinfarctions was significantly reduced in the timolol treated ex-smokers ($p < 0.01$) and in non-smokers ($p < 0.05$). The reduction in reinfarction rate among initial smokers treated with timolol or placebo was not significant.

EFFECT OF CHANGING SMOKING HABITS

Figure 1 shows the change in smoking habits during the first year of follow up in the two treatment groups. One month after the infarction the proportion of smokers had fallen from 52.5% to 21% in the placebo group, and from 54.7% to 22.7% in the timolol group; 58–60% of the smokers had therefore stopped smoking completely. In this analysis we did not take into account the amount of tobacco smoked. The smoking pattern remained remarkably constant during follow up. A non-significant increase from 22.7% one month after inclusion to 25.9% after one year was found in the number of smokers in the timolol group. There was little crossover between the smoking groups. Only one initial non-smoker became a smoker later, and 16 ex-smokers started smoking again during the first year. Changes in smoking habits were recorded one month after the change had occurred. One

hundred and ninety nine patients with a follow up of less than one month because of withdrawals (58 in placebo group, 81 in timolol group) or death (37 in placebo group, 23 in timolol group) were excluded from this analysis. A total of 1685 patients continued follow up, and Table 3 and Fig. 2 show the mortality and reinfarction rates.

Overall mortality was highest in placebo treated smokers (11.3%). Among those who continued smoking we found a significantly reduced incidence of early cardiac death in the timolol group compared with the placebo group (15 vs four, $p < 0.05$), a reduction of 75%, and of all deaths (20 vs nine, $p < 0.05$). In the non-smoking groups combined the reduction in incidence of early cardiac death was 47% (51 vs 26, $p < 0.01$) and of all deaths 40% (60 vs 35, $p < 0.05$) in the timolol group compared with the placebo group. Among ex-smokers the reduction in the incidence of early cardiac death in the timolol group compared with the placebo group was 63% (19 vs seven $p < 0.05$) whereas that in the incidence of all deaths was not significant. Treatment with timolol of those who stopped smoking (new ex-smokers) was associated with a reduction in total mortality of 39% (not significant) and early cardiac death by 39% (not significant). In the placebo treated patients cessation of smoking was associated with a reduction in total mortality of 26% (not significant).

We found a significant reduction in the incidence of initial reinfarctions in ex-smokers (27 vs 13, $p < 0.05$) and in all non-smokers combined (73 vs 47, $p < 0.05$) in patients treated with timolol. The reduction in incidence of reinfarctions among smokers was not significant (Table 3, Fig. 2b). Nevertheless, cessation of smoking reduced the reinfarction rate by 45% ($p < 0.05$) in placebo treated patients. Twenty six (14.7%) of 177 patients who continued smoking and 22 (8%) of 276 who ceased smoking had non-fatal reinfarctions during the study. In the new ex-smoker group the reinfarction rate was the same (8%) with or without timolol treatment. A placebo treated continued smoker had a more than twofold reinfarction rate compared with a timolol treated ex-smoker.

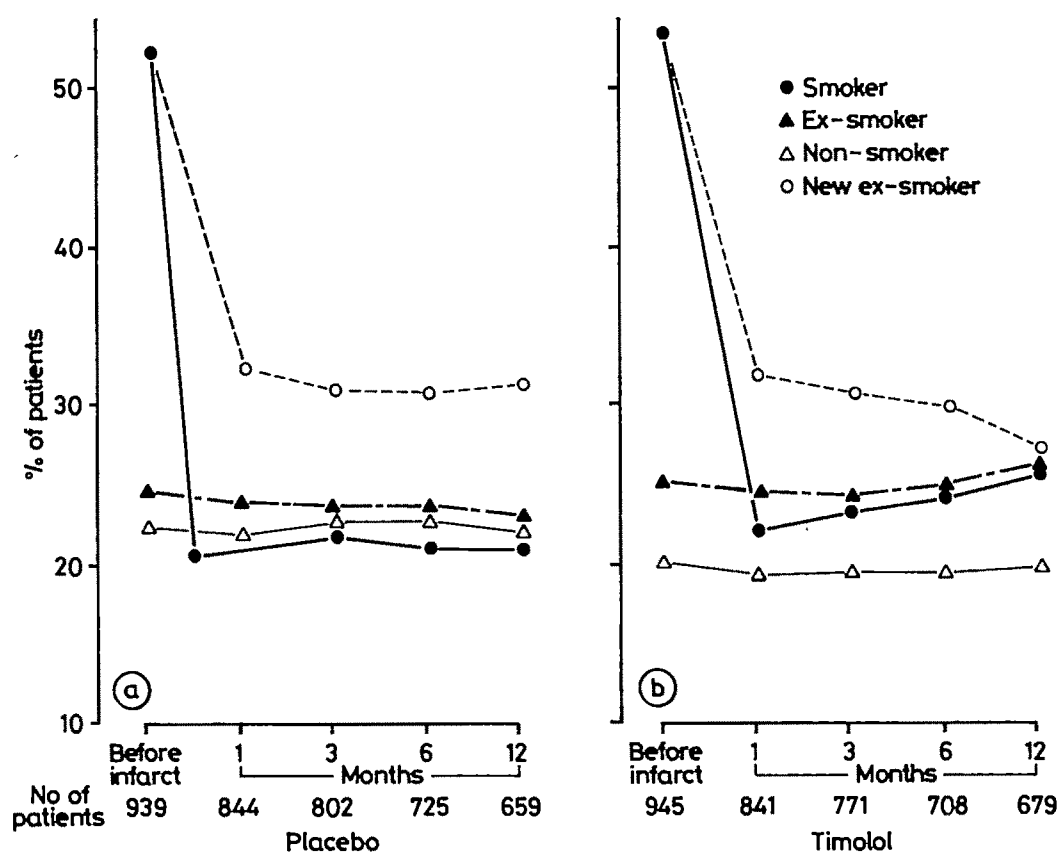


Fig. 1 Smoking habits during study in combined risk groups, treated with (a) placebo or (b) timolol.

Discussion

Of the men and women alive seven days after acute myocardial infarction and included in this study, 59.4% and 31% respectively were smokers. Of the total population of Norway at the time the study took place, 44% of men and 31% of women aged 16 to 74 years were reported to be smokers.⁴ The higher pro-

portion of smokers in the study population probably reflects the fact that smoking is a primary risk factor for coronary heart disease, although we did not record smoking data for the 48% of patients excluded out of the 3647 patients with myocardial infarction initially screened. Hospital mortality due to acute myocardial infarction has been reported to be higher in smokers than in non-smokers,⁵ decreasing the proportion of

Table 3 Frequency distribution of deaths and reinfarctions from second month of follow up. Figures are numbers (%) of patients

Category	Smoker		New ex-smoker		Ex-smoker		Non-smoker		Non-smoking groups combined	
	P	T	P	T	P	T	P	T	P	T
Total No of patients	177	191	276	275	204	207	187	168	667	650
Deaths during treatment or within 28 days of withdrawal										
Early cardiac death	15 (8.5)	4 (2.1)*	20 (7.2)	12 (4.4)	19 (9.3)	7 (3.4)*	12 (6.4)	7 (4.2)	51 (7.6)	26 (4.0)**
All deaths	20 (11.3)	9 (4.7)*	23 (8.3)	14 (5.1)	21 (10.3)	10 (4.8)	16 (8.6)	11 (6.5)	60 (9.0)	35 (5.4)*
Non-fatal reinfarctions during treatment or within 28 days of withdrawal	26 (14.7)	19 (9.9)	22 (8.0)	22 (8.0)	27 (13.2)	13 (6.3)*	24 (12.8)	12 (7.1)	73 (12.3)	47 (7.2)*

p<0.05, **p<0.01.

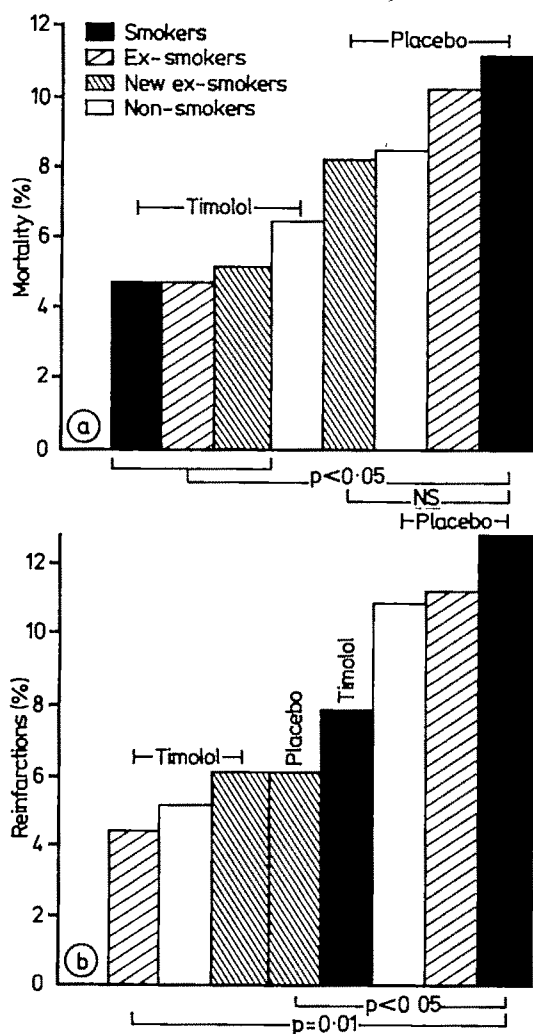


Fig. 2 (a) Total mortality and (b) reinfarction rate according to smoking habit in patients treated with timolol or placebo.

smokers among survivors of myocardial infarction. The association of smoking with the development of coronary heart disease is well known.⁵⁻¹⁴ The risk of coronary heart disease increases with the increasing amount smoked irrespective of other known risk factors—for example, hypertension or increased plasma cholesterol concentrations.¹⁵ The risk of coronary heart disease is unrelated to the years of exposure to smoking,⁶ which suggests an immediate and non-cumulative effect of tobacco smoking on the incidence of coronary heart disease.

In the present study the classification of patients into three risk groups probably correctly reflects the extent of myocardial damage.¹ As expected, the mor-

tality rate was highest in the patients with a recurrent infarction and lowest in patients with a first uncomplicated myocardial infarction. We did not find any significant differences in initial smoking patterns in patients surviving a first myocardial infarction with or without complications (risk groups 2 and 3). In risk groups 2 and 3, 56.2% and 54.7% respectively were initial smokers. The smoking pattern with regard to amount smoked or the duration of smoking was not different, although 9.3% of smokers in risk group 2 smoked >25 cigarettes a day compared with 5% in risk group 3. The proportion of smokers was smaller in patients with a recurrent infarction than in patients with a first myocardial infarction, probably reflecting the effect of smoking counselling after their previous myocardial infarction.

Smoking, together with serum lipid concentrations and blood pressure, is associated with the highest risk for coronary heart disease. Prospective epidemiological investigations have reported that smoking shows higher relative risk ratios among younger persons than older cohorts.^{9,11} The strong relation between smoking habits and age of survivors after acute myocardial infarction in this study may partly be due to more smokers of advanced age dying in the acute stage.

Several intervention studies have assessed the effect of stopping smoking in healthy persons. No significant effect of stopping smoking on death from coronary heart disease was reported by Rose and Hamilton and Rose *et al.*^{16,17} The Multiple Risk Factor Intervention Trial¹⁸ and the World Health Organisation European Collaborative Group¹⁹ reported a significant reduction in coronary heart disease and mortality when risk factors such as hypertension, smoking, high plasma cholesterol concentrations, and weight were reduced. A report from the Framingham Study showed that men who gave up smoking reduced their risk of coronary heart disease by a half.¹¹ Nevertheless, those subjects over 65 years derived no such benefit from giving up smoking. The Oslo Study Group reported a significant reduction in the incidence of myocardial infarction and sudden cardiac death when high serum cholesterol concentrations were controlled and smoking was reduced.²⁰

Cessation of smoking after myocardial infarction is associated with a significant reduction in cardiovascular mortality.²¹⁻²⁸ A 61% reduction in the mortality rate over a six year period was reported from the Framingham Study,²⁹ and a 55% lower 13 year mortality in those who stopped smoking after an episode of unstable angina or myocardial infarction compared with those who continued smoking was reported by Daly *et al.*³⁰ In all risk groups combined we found a highly significant reduction in total mortality and the incidence of early deaths in patients treated with

timolol. Although the observed reduction in total mortality of 26% in those who stopped smoking (and treated with placebo) did not reach statistical significance, it accords with the findings of earlier intervention studies.

Our analyses further suggest that the reinfarction rate is significantly lower among initial smokers who stop smoking and among initial non-smokers who are treated with timolol after the infarction.

Although assessment of the effect of treatment in separate subgroups should be regarded with caution, our observations suggest that the cessation of smoking enhances the effect to timolol treatment on mortality after acute myocardial infarction and is essential in substantially reducing the reinfarction rate.

We thank Leo Giezendanner for statistical assistance.

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Role of transient ischaemia and perioperative myocardial infarction in the genesis of new septal wall motion abnormalities after coronary bypass surgery

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SUMMARY To evaluate the role of ischaemia in the genesis of new septal wall motion abnormalities after coronary artery bypass surgery 45 patients were studied by cross sectional echocardiography before and 8-10 days after operation. Regional left ventricular wall motion was classified as normal, hypokinetic, akinetic, or dyskinetic. Septal wall motion abnormalities were correlated with electrocardiographic Q wave changes and serial serum MB creatine kinase measured before and 4, 7, 21, 48, and 72 hours after operation. Of the 14 patients who developed new septal wall motion abnormalities after operation two developed septal akinesis (both had perioperative infarction) and one new dyskinesis in the previously akinetic septal segment. Of the 11 patients with new septal hypokinesis, eight had normal serial creatine kinase MB values, two had raised values peaking four and seven hours after operation, with a return to normal values at 21 hours indicating transient ischaemia, and one had enzymatic criteria for perioperative infarction.

Most new echocardiographic septal wall motion abnormalities after coronary artery bypass grafting are not caused by transient ischaemia, perioperative infarction, or generalised cell necrosis.

A high incidence of new echocardiographic septal wall motion abnormalities has been detected after valvar heart surgery and coronary bypass surgery.¹⁻³ The mechanisms underlying such new septal wall motion abnormalities are, however, controversial.⁴ Some workers stress the role of pericardiotomy with secondary loss of pericardial restraint in the origin of these abnormalities,⁴ while others favour perioperative ischaemia.²

The purpose of this study was to define the importance of transient myocardial ischaemia and perioperative myocardial infarction in the causation of new echocardiographic septal abnormalities after coronary artery bypass surgery.

Patients and methods

Sixty three consecutive patients admitted for coronary artery bypass graft surgery were studied with cross

sectional echocardiography. Patients with unstable angina, left ventricular aneurysm, and additional non-coronary heart disease were excluded. Forty five (71%) patients (42 men, three women; age range 38-65 (mean (SD) 51 (7) years) had technically satisfactory cross sectional echocardiograms, defined by the visualisation of septal left ventricular wall segments in at least three left ventricular short axis and one apical two chamber views. Thus 18 patients were excluded because of technically inadequate preoperative echocardiographic studies.

Patients in the study group had exertional angina and severe two and three vessel coronary disease. Of these, 24 had a previous history compatible with myocardial infarction, and 27 had regional wall abnormalities on left ventricular angiography (right anterior oblique single plane). None had symptoms or physical signs of right or left heart failure.

Each patient admitted to the study underwent (a) routine 12 lead electrocardiography 24 hours before cardiac surgery and 8-10 days postoperatively, (b) cross sectional echocardiography 24 hours before and 8-10 days postoperatively, and (c) cardiac enzyme estimation, specifically of creatine kinase MB, before

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Accepted for publication 2 May 1985

operation (within 12 hours) and 4, 7, 48, and 72 hours after the end of cardiopulmonary bypass.

CARDIAC SURGERY

The surgical technique consisted of a median sternotomy and institution of cardiopulmonary bypass with bubble oxygenator, hypothermia (27–30°), and haemodilution (packed cell volume 20–25%). Pump flow was maintained at 2.0 l/m². Cold potassium cardioplegia was used for myocardial preservation. Reversed segments of saphenous veins were anastomosed to coronary arteries as appropriate. Proximal anastomoses were placed on the aortic wall under partial aortic clamping and during rewarming of the patient. Each patient received between two and six grafts (mean 3.4) and 13 patients underwent grafting and endarterectomy. Mean aortic cross clamping time ranged from 25 to 85 (mean 46) minutes and bypass time ranged from 59 to 125 (mean 84) minutes.

CROSS SECTIONAL ECHOCARDIOGRAPHY

All studies were performed using a mechanical sector scanner (ATL Mark 1, Squibb Medical Systems) with a 2.25 MHz transducer. Each study was performed from standard parasternal, apical, and subcostal views and the patient was positioned to obtain the optimum images from each window. Images were recorded on a videotape for subsequent review and analysis. Each study was analysed by two independent observers. Where disagreement occurred a consensus was reached. Each study included at least three adequate short axis views in which more than 75% of the entire endocardial and epicardial outline but including the septum was visible throughout systole and diastole.

Segmental wall motion analysis was performed by dividing the left ventricle into five segment according to the classification of Kisslo *et al.*⁵ In this analysis,

anterolateral, posterior, inferior, apical, and septal segments are identified from the three different transducer positions used. Anterolateral, posterior inferior, and septal segments are analysed from the 3–5 short axis views of the left ventricle recorded at the level of at least three of the following: (a) mitral valve leaflet; (b) papillary muscle tip; (c) papillary muscle body; (d) papillary muscle base; and (e) left ventricular apex. The apical segment is also assessed from the apical two chamber view. Regional left ventricular wall motion was graded for the septum by a modification of the terminology of Herman and Gorlin: 3, normal; 2, hypokinetic; 1, akinetic; and 0, dyskinetic.⁶ As with qualitative angiographic analysis, wall motion in the septal segment was judged relative to the motion of other segments.

CARDIAC ENZYME ESTIMATION

Total creatine kinase activity was measured at 37°C by the Scandinavian recommended method with *N*-acetyl cysteine activation.⁷ All the results of creatine kinase and creatine kinase MB assays were tabulated according to the time of collection and the mean and standard deviations were calculated.

DEFINITIONS

ECG evidence of myocardial infarction—Q waves broader than 0.04 s in precordial or inferior leads were considered to be abnormal.⁸

Abnormal enzyme release—Creatine kinase MB release, indicating perioperative myocardial infarction, was defined as a peak activity in the serum of >50 IU/l within 21 hours of operation.⁹ The time of maximal creatine kinase MB activity was expressed in hours after the end of cardiopulmonary bypass. Transient reversible myocardial ischaemia was defined as a serum peak ≥ 40 IU/l 4–7 hours after

Table Results in 14 patients with new septal wall motion abnormalities after coronary artery bypass surgery (CABG)

Case No	Echocardiography Septal wall motion		Pericardial effusion	ECG changes after CABG	Creatine kinase MB activity (IU/l)				Findings after CABG
	Before	After			Before	After (hour*)	4	7	21
1	Normal	Hypokinetic	—		6	22	5	6	Normal wall motion
2	Normal	Hypokinetic	+	ST-T	2	0	13	4	Normal wall motion
3	Normal	Hypokinetic	+		6	48	30	20	Transient ischaemia
4	Normal	Hypokinetic	+	ST-T	8	14	8	2	Normal wall motion
5	Normal	Hypokinetic	+		10	10	2	4	Normal wall motion
6	Normal	Hypokinetic	+		2	6	2	6	Normal wall motion
7	Normal	Hypokinetic	+	ST-T	4	8	26	76	Myocardial infarction
8	Normal	Hypokinetic	+		12	86	86	32	Transient ischaemia
9	Normal	Hypokinetic	—	ST-T	4	32	30	24	Normal wall motion
10	Normal	Akinetic	—	ST-T	4	14	26	66	Myocardial infarction
11	Normal	Hypokinetic	+	ST-T	8	10	2	4	Normal wall motion
12	Normal	Hypokinetic	+	ST-T	4	20	28	4	Normal wall motion
13	Akinetic	Dyskinetic	+		4	28	16	20	Normal wall motion
14	Normal	Akinetic	—	QS (V1–V4)	10	14	2	124	Myocardial infarction

*After the end of extracorporeal circulation.

—, absent; +, present

operation with normal activity at 21 hours.⁹

New postoperative septal motion abnormality was defined as a change in septal segment score of ≥ 1 in the postoperative echocardiographic short axis view showing the maximum change in wall motion score.

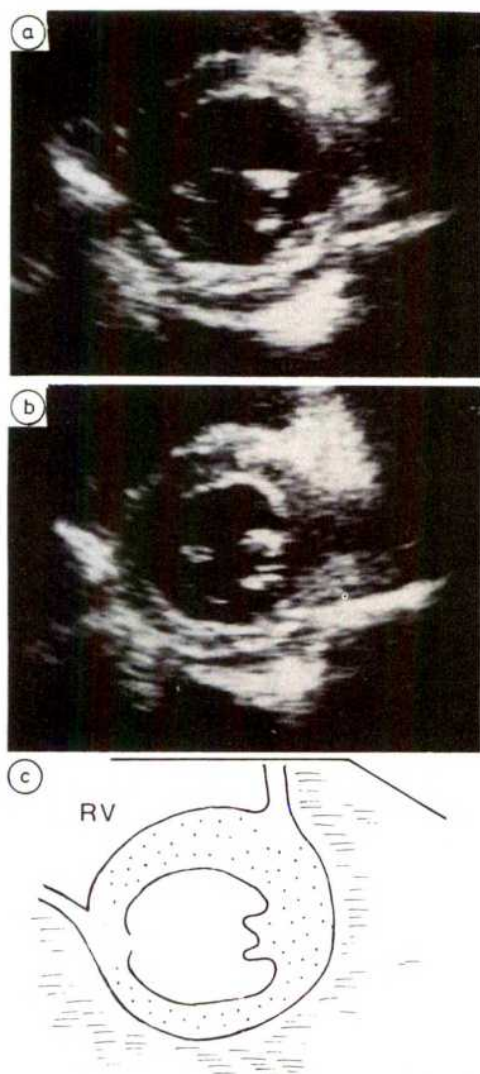


Figure Cross sectional echocardiographic short axis view of the left ventricle at the level of the papillary muscle tip. (a) Diastolic and (b) systolic stop frames show the echocardiographic study quality required to detect the septal endocardial signal so that (a) endocardial motion and (b) wall thickening can be described. This figure represents the average study quality in a patient who was classified as having normal septal wall motion preoperatively.

STATISTICAL ANALYSIS

Means and standard deviations were calculated in the usual way. Paired *t* tests were used to test the difference between the means.

Results

ECHOCARDIOGRAPHY

Of the 45 patients with technically adequate preoperative echocardiograms 34 had septal segments that showed normal regional wall motion. Figure 1 shows a typical normal study. Eleven patients had septal segments that showed abnormal wall motion. Of these, five had hypokinetic segments, four akinetic, and two dyskinetic. The preoperative regional wall motion index was 2.58 (0.84) (mean (SD)). After operation, the index for the 45 patients decreased to 2.14 (0.83) ($p < 0.001$). Thirty (67%) septal segments were unchanged in the postoperative study, 14 had deteriorated, and one improved.

Segments deteriorated (Table)

Akinesis—Of the 14 septal segments that deteriorated, two showed new akinesis after normal preoperative motion. Both patients had perioperative myocardial infarction based on creatine kinase MB criteria, but only one patient had new electrocardiographic Q waves.

Hypokinesis—Eleven segments became hypokinetic postoperatively after preoperative motion had been normal. Of these, eight had normal serial creatine kinase MB values after operation and two had an abnormal rise in enzyme activity without electrocardiographic ST-T wave changes. Creatine kinase MB values peaked between four and seven hours in these patients but were within normal values at 21 hours, indicating transient ischaemia.¹⁰ In one of the 11 patients activity peaked at 21 hours, and this patient was considered to have perioperative myocardial infarction.⁹

Dyskinesis—One segment that had been akinetic before operation became dyskinetic. This patient had no electrocardiographic or enzymatic change.

A total of 11 patients therefore had new septal abnormalities but no enzymatic or electrocardiographic evidence of perioperative myocardial infarction; nine had an associated mild or moderate pericardial effusion.

Segments improved

Only one preoperatively abnormal septal segment improved, from dyskinetic to akinetic. This was not associated with pericardial effusion or an abnormal rise in creatine kinase MB activity. Of the 10 other septal segments that were abnormal preoperatively, none showed any change in the postoperative study.

Discussion

We detected a high incidence (24%) of new septal wall motion abnormalities after coronary bypass surgery in our patients. Although ischaemic damage may have been responsible for septal hypokinesia in two patients and perioperative infarction may have occurred in three patients, perioperative infarction and transient ischaemia were not the cause of most of these new septal abnormalities. Experimental studies have shown that brief periods of ischaemia can depress myocardial function. This injury is reversible with time, although the structural, metabolic, and functional properties of the myocardium may remain severely disturbed for days before recovery.^{10,11} This phenomenon may explain the late normalisation of surgically induced septal wall motion abnormalities in one patient reported by Rubenson *et al* studied some weeks after operation.¹² Our results, however, support a recent radionuclide study of patients with abnormal septal wall motion after coronary bypass surgery, who had normal thallium-201 perfusion scans of this region.¹³ Our findings of normal enzyme patterns in most patients with new abnormal septal motion support the notion that factors other than ischaemia or infarction are operating.

We found an association between septal hypokinesia and pericardial effusion. Several explanations for this phenomenon are possible. Septal hypokinesia has been reported in patients with constrictive pericarditis and with major pericardial effusion.^{14,15} In some of our patients therefore the presence of a moderate sized pericardial effusion may have been responsible for the septal abnormality. We have also noted abnormal echoes that appear to represent organised clot in part of the anterior right ventricular wall in most patients after coronary artery bypass surgery. These clots may therefore contribute to the abnormal septal wall motion without there necessarily being an additional large pericardial effusion. Recent intraoperative echocardiographic studies suggest that the pericardiotomy itself is responsible for septal wall motion disturbances secondary to excessive anterior cardiac mobility.⁴ This finding is supported by reports that septal hypokinesia is seen in patients with congenital absence of the pericardium.¹⁶ At our institution the pericardium is always left open but does not remain so since subsequent healing and a variable amount of epicardial and mediastinal adhesion inevitably occurs. This is consistent with the observation that most septal abnormalities tend to return to normal with time,¹³ and indeed Righetti *et al* speculated that postoperative adhesions could lead to late normalisation of septal wall motion.²

Echocardiographic septal hypokinesia has also been reported after valve surgery.¹ Ventriculotomy cannot

be implicated as a possible mechanism since septal hypokinesia is not seen in patients undergoing mitral valvotomy.¹ Furthermore, septal abnormalities have been found in patients undergoing cardiac surgery without a ventriculotomy.^{1,2} Although all our patients had septal hypokinesia or akinesia, none had associated right ventricular volume overload or electromechanical,¹⁷ structural,¹⁸ or other pathophysiological¹⁹ conditions that are known to be associated with abnormal septal wall motion.⁷

In two patients perioperative myocardial infarction resulted in new septal akinesia with an abnormal rise (>50 IU/l) in serum creatine kinase MB activity 21 hours after the end of cardiopulmonary bypass indicating irreversible myocardial damage.⁹ A few of our patients with new septal hypokinesia showed an abnormal rise in creatine kinase MB activity peaking between four and seven hours but with normalisation at 21 hours indicating transient ischaemia. Creatine kinase MB is a very sensitive chemical indicator of myocardial damage, and abnormal rises in its activity are detected after episodes of stable and unstable angina.²⁰ The qualitative detection on single quantitation estimates of the enzyme by itself is, however, not specific for the diagnosis of perioperative infarction.^{21,22} Histochemical and ultrastructural studies have shown that the cellular changes after cardiopulmonary bypass grafting closely resemble changes seen after reperfusion of ischaemic regions.²³ This ischaemic insult may result in changes in myocardial cell permeability,²⁴ which in turn could lead to a "stunned" septal segment.¹⁰ It is reasonable to suppose therefore that changes in membrane permeability promote cellular depletion of creatine kinase MB.^{20,22}

In conclusion this study has shown that transient myocardial ischaemia or generalised cell necrosis are not responsible for the majority of new septal wall motion abnormalities after coronary bypass graft surgery. New echocardiographic septal wall akinesia may be a marker of perioperative infarction but appears to be most frequently associated with intrapericardial collections.

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Does left ventricular aneurysmectomy improve ventricular function in patients undergoing coronary bypass surgery?

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SUMMARY Fourteen consecutive patients undergoing left ventricular aneurysmectomy and coronary artery bypass grafting were studied by multiple gated ventricular scintigraphy at rest and during exercise before and at six weeks and six months after surgery. All had congestive heart failure and 12 angina pectoris. Before operation left ventricular ejection fraction fell significantly with exercise, as did the regional wall motion score. Six weeks after surgery all surviving patients were free of angina, with an improvement in functional class; the total exercise workload improved significantly, but resting left ventricular ejection fraction was unchanged; the regional wall motion score improved in both the anterior and left anterior oblique projections, although extensive areas of abnormal contraction persisted. Exercise left ventricular ejection fraction improved significantly after operation at six weeks, and previous exercise induced abnormalities of regional contraction were abolished. Six months after operation angina pectoris had recurred in one patient, but there was no further change in ventricular function in the remainder.

Although resting ejection fraction is not improved, symptoms, exercise workload, and exercise ventricular function can be improved by aneurysmectomy and coronary artery bypass grafting, but the respective contribution of these two procedures remains uncertain.

Left ventricular aneurysm is a well recognised and important complication of myocardial infarction. The incidence after infarction varies widely, owing to differing diagnostic criteria but is between 2% and 15%.¹⁻⁴ Its clinical course is variable, carrying a poor prognosis with generally a high morbidity due to angina, congestive heart failure, or atrial arrhythmias.^{5,6} Five year survival rates of between 12% and 27% have been reported,^{1,2} and the mean time from infarction to death has been quoted at 4.8 years.⁷ More recent reports have shown an improved survival rate of 71% at four years; there appears to be no difference in the mortality rate between those patients with aneurysms and those without, given an equal degree of left ventricular dysfunction.⁸

Since Cooley *et al* first described the successful excision of a left ventricular aneurysm⁹ this operation has been widely performed in patients whose symptoms have not been adequately controlled by medical treatment. Long term symptomatic improvement

after aneurysmectomy has been reported¹⁰⁻¹² but not without an appreciable operative risk, the early mortality rate being 6-22%.^{6,12-14} Despite these reports of symptomatic benefit a need exists for more objective studies of left ventricular function before and after surgery.

The purpose of our prospective study was to assess left ventricular function in a consecutive group of patients referred for elective surgery of their postinfarction aneurysm and to correlate these findings with the symptomatic state of the patient. All had multivessel coronary artery disease and underwent additional myocardial revascularisation. Patients were studied before and six weeks and six months after surgery by multiple gated ventricular scintigraphy both at rest and during dynamic supine exercise. This method provides a non-invasive, geometrically independent method of assessing serial left ventricular function.

Patients and methods

STUDY POPULATION

Fourteen consecutive patients (13 men, one woman; mean age 51.7 (range 38-69) years) referred for elec-

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Accepted for publication 19 March 1985

tive surgery of postinfarction left ventricular aneurysm were studied prospectively. Nine patients presented with symptoms of congestive heart failure and angina pectoris, three with angina, and two with congestive heart failure alone. No patient had detectable atrial arrhythmia or evidence of systemic embolism. Thirteen (93%) patients had electrocardiographic or enzymatic confirmation or both of previous myocardial infarction, with a mean of 1.4 (range 1–3) infarcts per patient, the last a mean of 17.5 (range 3–60) months before investigation.

Eleven patients had severe proximal three vessel disease and 12 total occlusion of the left anterior descending coronary artery. Four patients had a $\geq 50\%$ left main stem stenosis (Table 1). All patients had a discrete anteroapical aneurysm diagnosed by contrast angiography. This was defined as the presence of an akinetic segment outside the expected margins of the left ventricle or a localised protrusion of an area of the left ventricle outside the expected margins during systole. No patient had associated mitral regurgitation.

Medication was not withdrawn before the preoperative investigation owing to the risk of exacerbating symptoms.^{15–17} Table 2 shows the treatment given before and after surgery.

MULTIPLE GATED VENTRICULAR SCINTIGRAPHY
Multiple gated ventriculography based on techniques previously described¹⁸ was performed at rest and during dynamic supine exercise. Imaging was started at the onset of symptoms—namely, angina, dyspnoea, fatigue, or electrocardiographic evidence of ischaemia (>1 mm ST segment depression). Blood pressure was recorded at rest and at one minute intervals throughout the exercise study; heart rate and cardiac rhythm were monitored throughout. The study was terminated if angina became progressively severe or haemodynamic deterioration or serious arrhythmia occurred. The same symptom limited protocol was repeated six weeks and six months after surgery. Data acquisition time was, on average, six minutes.

Ventricular function was assessed both in terms of global ejection fraction and abnormalities of regional contraction.¹⁸ Left ventricular wall motion was assessed in both anterior and left anterior oblique projections by reviewing the scintigraphic data in a closed loop cine format. Semiquantitative assessment was performed by dividing the left ventricle into five segments. In the anterior projection the ventricle was divided into anterobasal, anterolateral, apical, diaphragmatic, and posterobasal segments. In the oblique projection division was into proximal and distal

Table 1 *Distribution and percentage stenoses of proximal coronary artery disease and number of vessels subsequently undergoing coronary bypass grafting*

Case No	Coronary anatomy (% stenosis)				Graft sites		
	LMS	LAD	Cx	RCA	LAD	Cx	RCA
1	—	100	75	Occluded	1	—	1
2	50	100	75	75	—	2	—
3	—	100	75	75	—	1	1
4	—	100	75	75	—	1	—
5	—	100	75	$<50^*$	—	1	—
6	—	100	75	$<50^*$	—	1	1
7	—	100	75	$<50^*$	—	1	—
8	—	100	75	75	—	2	1
9	100	—	—	75	—	1	1
10	—	90	75	100	—	1	1
11	50	100	75	75	—	1	1
12	—	100	75	75	—	1	—
13	50	90	75	75	—	2	—
14	—	100	75	75	—	—	1

LMS, left main coronary artery, LAD, left anterior descending coronary artery; Cx, circumflex system; RCA, right coronary artery.

*Diffuse disease

Table 2 *Drug treatment before and after surgery in patients undergoing left ventricular aneurysmectomy and coronary bypass grafting*

	Before surgery (n=14)	After surgery	
		At 6 weeks (n=13)	At 6 months (n=11)
Digoxin	6	12	5
Diuretics	6	13	9
Beta blockers	8	1	1
Calcium antagonists	3	1	—
Disopyramide	—	1	1
Warfarin	5	7	5
Long acting nitrates	8	—	—

septal, inferior, and proximal and distal posterolateral segments. Each segment was assigned a value ranging from 3 for normal contraction to 0 and -1 for akinesia and paradoxical contraction respectively. The total regional wall motion score was obtained by the summation of these segmental values in each projection.

SURGERY

Surgery was undertaken using cardiopulmonary bypass with cold cardioplegia and topical hypothermia for myocardial protection together with moderate systemic hypothermia (30°C). Mean bypass time was 91.7 (range 80–109) minutes and ischaemic time 69.1 (range 48–139) minutes. At operation a discrete anteroapical aneurysm was confirmed in all 14 patients. Excision of the aneurysm was undertaken leaving a cuff of scarred fibrous tissue distal to the demarcation between normal muscle and scar tissue in order to ensure adequate suturing on closure of the resulting ventriculotomy.

All patients had coronary artery bypass grafting in addition to excision of the aneurysm. Twelve patients received grafts to the circumflex system, including eight with additional grafts to the right coronary artery (Table 1).

STATISTICS

All data are presented as arithmetic means (standard error of the mean (SEM)). Differences were tested for significance by the paired *t* test and the Wilcoxon signed rank sum test. *P* values >0.05 were regarded as not significant.

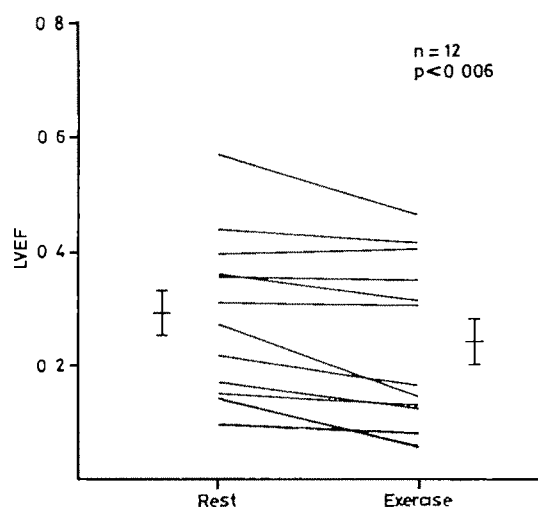


Fig. 1 Left ventricular ejection fraction (LVEF) response to exercise before left ventricular aneurysmectomy and coronary artery bypass grafting. Bars denote mean (SEM).

Results

PREOPERATIVE INVESTIGATION

Resting studies were performed in all 14 patients and exercise studies in 12. Two patients felt unable to perform the exercise study. The mean functional class (New York Heart Association criteria)¹⁹ was 3.1. Resting ejection fraction was 0.29(0.04). The exercise workload achieved was 1413(100) kpm (230.8(16.3) W). Seven patients were taking beta blocking drugs; their heart rate and systolic blood pressure rose from 61 beats/min and 117 mm Hg to 66 beats/min and 118 mm Hg respectively. Five patients were not taking beta blockers; their heart rate and systolic blood pressure rose from 87 beats/min and 112 mm Hg to 104 beats/min and 125 mm Hg respectively. The response to exercise in the patients before operation was abnormal, exercise ejection fraction falling to 0.24(0.04) ($p < 0.006$) (Fig. 1), representing a relative fall in ejection fraction during exercise of 18.9(5.4)%. Likewise the regional wall motion score fell from 2.8(0.5) at rest, to 1.2(0.5) during exercise ($p < 0.001$). Ten patients showed exercise induced abnormalities of regional contraction confined to the posterolateral

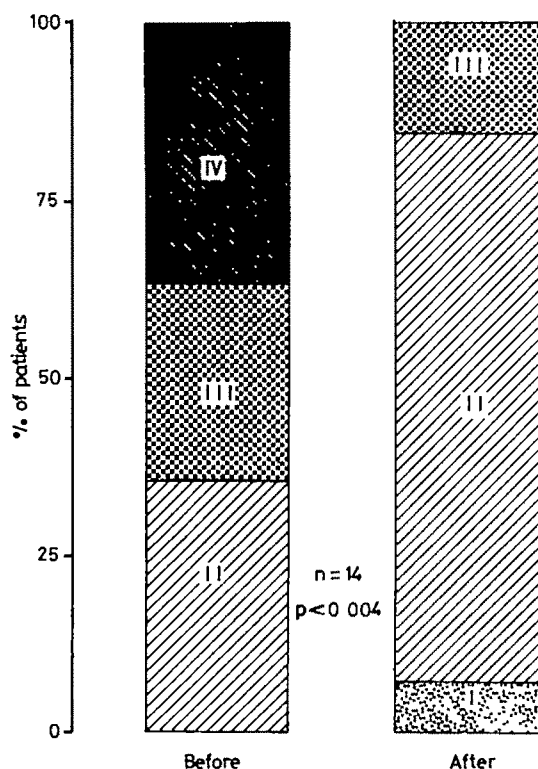


Fig. 2 Change in NYHA functional class before and after (six weeks) operation.

wall. Two patients showed no deterioration in regional contraction during exercise but both had a fall in global ejection fraction. No serious arrhythmias were encountered during exercise.

POSTOPERATIVE INVESTIGATIONS AT SIX WEEKS

One patient died three days postoperatively of a myocardial infarction sustained during the perioperative period, giving a hospital mortality of 7.1%. All 13 survivors were available for follow up.

The mean functional class improved to 2.1 ($p < 0.004$) (Fig. 2). All patients underwent an exercise study. None experienced angina but all were limited by dyspnoea and fatigue. The exercise workload improved to 2825(256) kpm (461.6(41.8) W) ($p < 0.001$) (Fig. 3a). One patient was taking beta blockers; his heart rate and systolic blood pressure rose from 76 beats/min and 115 mm Hg to 96 beats/min and 134 mm Hg respectively. Twelve patients were not taking beta blockers; their heart rate

and systolic blood pressure rose from 84 beats/min and 118 mm Hg to 113 beats/min and 147 mm Hg respectively. No serious arrhythmias were encountered.

The response of the resting left ventricular ejection fraction to surgery was variable (Fig. 4(a) and (b)). As a group, however, resting ejection fraction was unchanged at 0.32(0.03) (NS). During exercise, ejection fraction increased to 0.34(0.04) ($p < 0.04$) (Fig. 4(c) and (d)), representing a relative increase of 14.1 (3.2)% compared with a preoperative fall of 18.9 (5.4)% in this group of patients ($p < 0.002$).

Resting regional wall motion score in the anterior projection improved after operation from 3.1(0.4) to 6.0(0.6) ($p < 0.001$), and in the oblique projection from 2.7(0.5) to 4.2(0.6) ($p < 0.001$). Despite the apparent improvement in regional contractility extensive regional wall motion abnormalities remained after operation and were evident in both projections (Table 3). During exercise the previously induced abnormalities

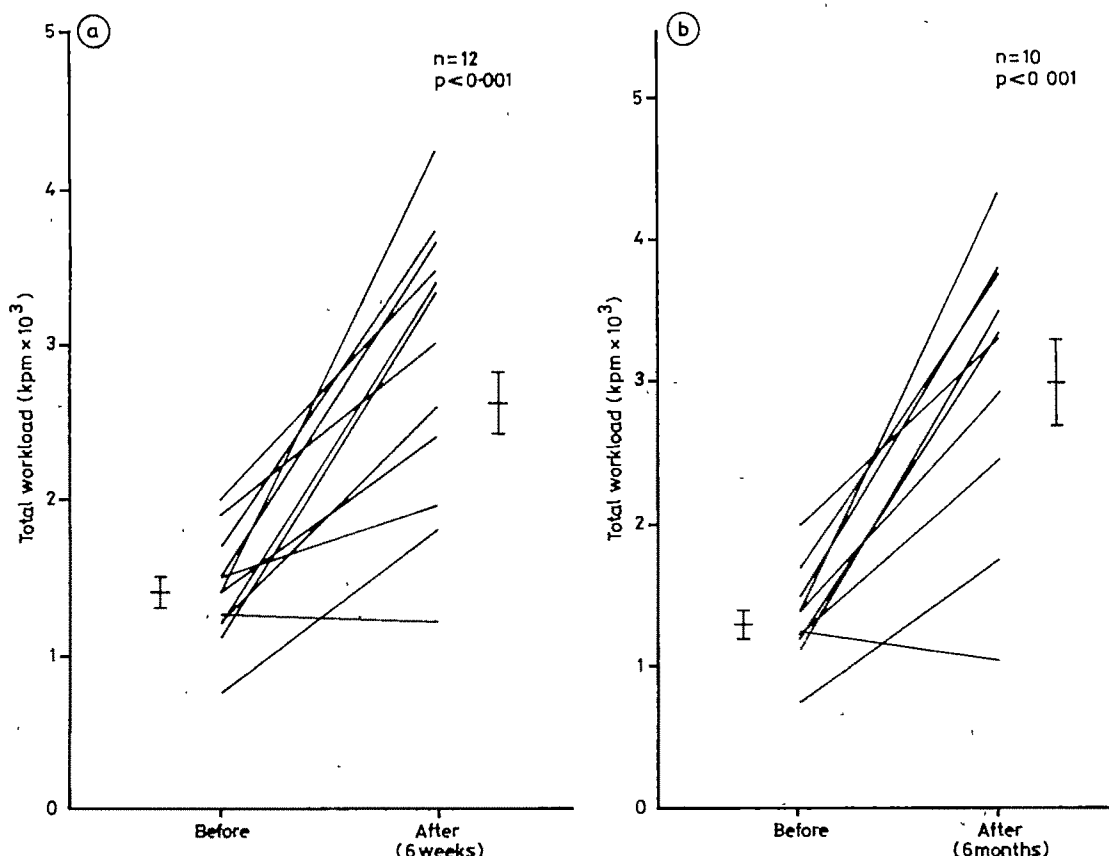


Fig. 3 Total exercise workload (a) before and six weeks after and (b) before and six months after operation. Bars denote mean (SEM). Conversion: traditional to SI units—workload: 1 kpm $\approx$ 6.12 W.

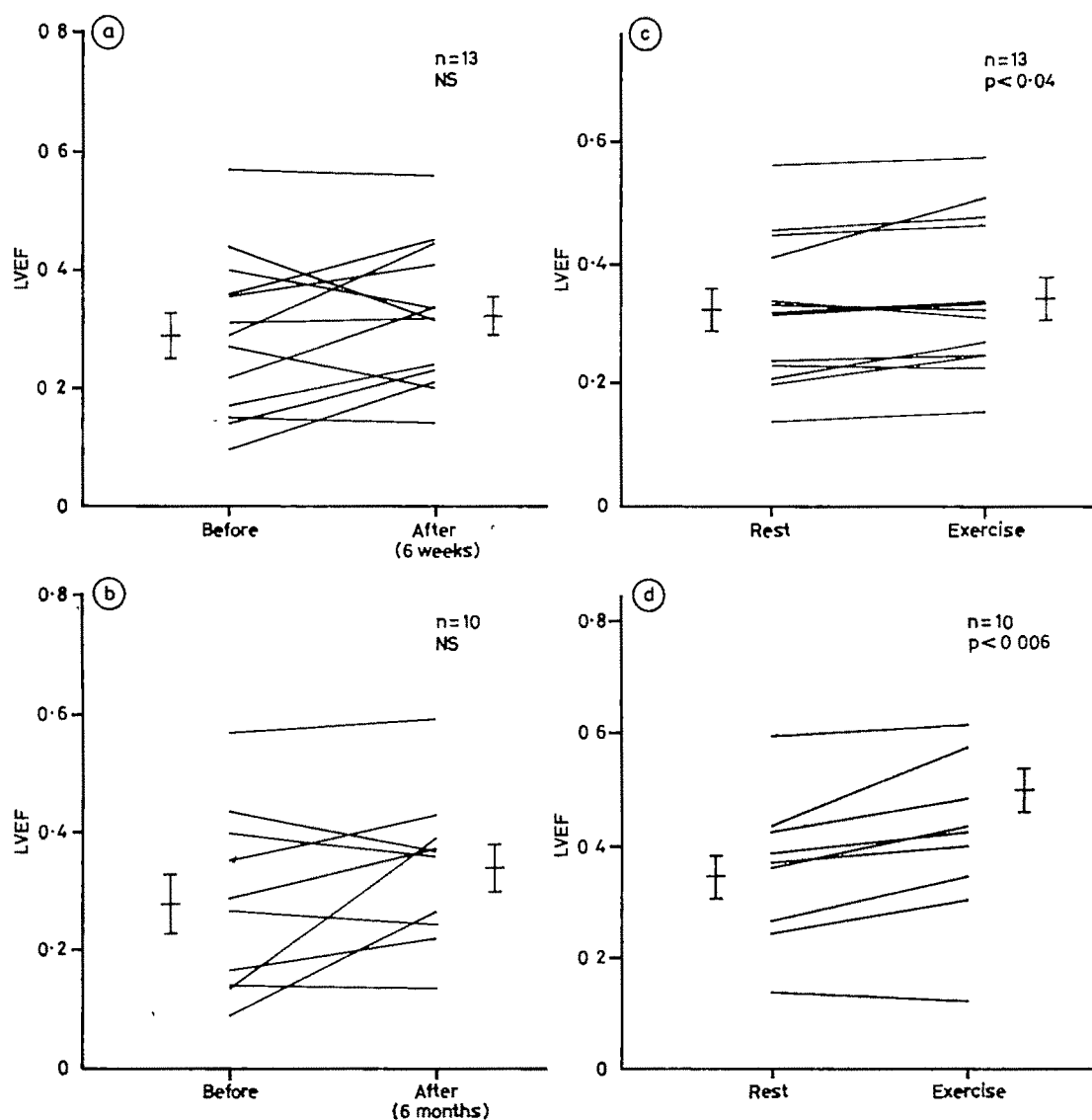


Fig. 4 Resting left ventricular ejection fraction (LVEF) (a) before and six weeks after and (b) before and six months after and left ventricular ejection fraction response to exercise (c) six weeks and (d) six months after left ventricular aneurysmectomy and coronary artery bypass grafting in surviving patients free of angina. Bars denote mean (SEM).

Table 3 Number of abnormally contracting segments remaining in surviving patients free of angina six weeks and six months after operation. Preoperative values for the same group of patients are shown in brackets

View	Severe hypokinesia	Akinesia	Paradox
<i>Six weeks (n=13)</i>			
Anterior	25 (11)	16 (23)	0 (12)
Left anterior oblique	15 (8)	30 (28)	1 (11)
<i>Six months (n=10)</i>			
Anterior	22 (9)	9 (17)	0 (11)
Left anterior oblique	12 (4)	23 (23)	1 (9)

of contraction were abolished, and there was no deterioration in the regional wall motion score.

POSTOPERATIVE INVESTIGATIONS AT SIX MONTHS

At further reinvestigation six months after operation two more patients had died of further infarction, giving a mortality rate of 21.4% at six months. Of the 11 surviving patients available to follow up, 10 had no angina but were limited only by dyspnoea and fatigue. One patient had a recurrence of angina, although to a lesser extent than preoperatively. The mean functional class of the patients free of angina was unchanged.

In the group of 10 patients free of angina, although the exercise workload of 3060(343) kpm (500(56) W) showed only a small insignificant increase over the six weeks value, it remained a significant increase over that achieved before operation ($p < 0.001$) in the same group of patients (Fig. 3). One patient was taking beta blockers; his heart rate and systolic blood pressure rose from 78 beats/min and 110 mm Hg to 100 beats/min and 140 mm Hg respectively. Ten patients were not taking beta blockers; their heart rate and systolic blood pressure rose from 75 beats/min and 119 mm Hg to 100 beats/min and 146 mm Hg respectively.

The response of the resting ejection fraction was again variable (Fig. 4) showing an increase in six patients and a fall in five compared with the preoperative values. As a group, however, it remained unchanged at 0.34(0.04) (NS).

The resting regional wall motion score in the anterior projection was 6.4(0.8) and in the oblique projection 4.1(0.6). This represented an improvement over the preoperative values ($p < 0.001$) but no significant change from the values obtained six weeks after operation. Extensive areas of regional dysfunction still remained (Table 3).

In patients free of angina, ejection fraction during exercise increased to 0.40(0.05) ($p < 0.006$) (Fig. 4), representing an 11.5(4.6)% increase in relative ejection fraction compared with a 20.9(6.9)% fall in the same group of patients preoperatively ($p < 0.002$). The regional wall motion score remained unchanged during exercise, the preoperative exercise induced abnormalities having been reversed. No serious arrhythmias were encountered.

One patient experienced recurrence of angina, although clinically less severe than before operation. He maintained his improved functional class and achieved a greater exercise workload than before operation. His global left ventricular response to exercise workload was again abnormal, the ejection fraction falling from 0.31 to 0.24 during exercise, with hypokinesia developing in the posterolateral wall and

a fall in the regional wall motion score. The resting ejection fraction was unchanged from the six weeks value.

Discussion

Resection of a left ventricular aneurysm has become an important form of treatment for those patients whose symptoms are not adequately controlled by medication. Many studies have reported the relief of symptoms after operation in selected cases,^{16 14} but few have examined serial left ventricular function and most are retrospective; for accurate evaluation of a procedure all patients undergoing surgery should be assessed prospectively. Several studies have included data at varying intervals after operation with some in the early postoperative period when adrenergic overactivity is known to influence ventricular function.²⁰ This makes the results difficult to interpret. The results of those studies assessing left ventricular function at rest have been conflicting; some show improvement after operation^{10 21 22} while others do not.^{11 23 24} Fewer studies have examined the effect of aneurysmectomy on exercise left ventricular function as judged by conventional angiography although two have shown no improvement in exercise function after operation.^{22 24} In our study a prospective consecutive series of patients was evaluated at rest and during exercise by a non-invasive technique at standard time intervals after operation, the earliest being six weeks when most of the effects of surgery have worn off.

In keeping with previous studies^{6 10 12} all our patients surviving six weeks showed symptomatic improvement and a pronounced increase in exercise tolerance, which was maintained at six months after operation. During the preoperative investigation beta blocking drugs were not withdrawn because of the risk of exacerbating angina.¹⁵⁻¹⁷ This might have affected our results; beta blocking drugs can have a negative inotropic effect on ventricular function.²⁵⁻²⁷ In patients with ischaemic heart disease, however, these drugs have been shown to have little detrimental effect on ventricular function even in those with a low ejection fraction.²⁸ Moreover improvement in ventricular function has been reported,^{29 30} as in patients with congestive cardiomyopathy.³¹ Thus we believe that the administration of these drugs before operation is likely to have had little influence on our results.

Resting ejection fraction remained abnormal after operation and was unchanged from the preoperative value both at six weeks and six months. Nevertheless, the individual results varied, some showing improvement and others none. This is in contrast to the study of Dymond *et al.*, which showed an overall improvement in resting left ventricular ejection fraction after aneurysmectomy.²² Direct comparison with our study

is difficult since Dymond's series of 12 patients included eight with single vessel disease; only two underwent myocardial revascularisation. This is in contrast to our series, most of whom presented with angina in addition to congestive failure and all of whom underwent coronary artery bypass grafting.

In theory, aneurysmectomy should reduce end diastolic and end systolic volumes equally, resulting in an increase in ejection fraction. Failure to achieve this could be due to insufficient resection of the aneurysm. The aneurysms in our patients were, however, resected to the transitional zone, leaving just a rim of fibrous scar tissue to support the sutures. An alternative suggestion is that destruction of the hypokinetic transitional zone by the sutures might render it akinetic²³; this also seems implausible because it was not our surgical practice. Most probably, the failure to demonstrate an improvement in overall ejection fraction in our patients was due to the insensitivity of radionuclide ventriculography in such dilated hearts. This is quite consistent with a useful improvement in cardiac output; for example, a 33% increase in stroke volume from 45 to 60 ml can be achieved with only a 5% increase in ejection fraction from 0.15 to 0.20 in a heart with an end diastolic volume of 300 ml. The improvement in regional contractility was largely accounted for by the resection of the paradoxically moving aneurysm (score -1) leaving instead an akinetic segment (score 0). Despite the improved wall motion score extensive areas of regional dysfunction remained and serious impairment of ventricular contraction persisted.

The improvement in exercise tolerance of those patients free of angina after operation was paralleled by an improvement in exercise ventricular function as we have reported previously.¹⁸ The deterioration in global ejection fraction induced by exercise preoperatively was corrected, although the increase was less than that expected for a normal ventricle. The exercise induced abnormalities of regional contraction were abolished after operation indicating that coronary bypass grafting corrected the ischaemic response in the remaining viable myocardium. Again direct comparison with the only two previous reports of exercise left ventricular function after aneurysmectomy^{22, 24} is difficult. Dymond's series²² has been discussed. Froehlich *et al*'s series,²⁴ like ours, contained mainly patients who had multivessel disease and presented with both angina and congestive cardiac failure. Unlike our patients, all of whom underwent aneurysmectomy, only 11 of 18 patients in their series underwent resection of the aneurysmal segment; in four it was plicated and in three no discrete aneurysm was found at operation, and so no direct surgery on the ventricle was undertaken. Postoperatively only 12 of 18 patients underwent exercise evaluation of ven-

tricular function, nearly a third of whom continued to experience angina with significant electrocardiographic ST segment depression. This suggests that continuing ischaemia during exercise adversely affected left ventricular function. In our series all patients at six weeks and all but one at six months were free of angina and showed no electrocardiographic evidence of ischaemia during exercise. The single patient with angina at six months was analysed separately.

Of the patients who showed preoperative evidence of reversible ischaemia, the site was localised to the posterolateral wall of the left ventricle in all cases and the wall motion abnormality was abolished by coronary grafting. This emphasises the value of radionuclide ventriculography both in assessing the functional reserve of the remaining viable myocardium and in providing information about which vessel to graft. Furthermore posterolateral wall function should be examined because it has been shown to be an important determinant of mortality associated with resection of anteroapical aneurysm.³²

Many early reports stress the poor long term prognosis of medically treated patients with ventricular aneurysm but a recent long term evaluation of a large group of patients with postinfarction ventricular aneurysm⁸ has shown no difference in mortality between patients with an aneurysm and those without, given an equal degree of left ventricular function. This in turn suggests that a left ventricular aneurysm has no independent influence on survival. Furthermore, the lack of improvement in resting ejection fraction after aneurysmectomy, as shown in our study, implies that operation is unlikely to improve prognosis in patients like ours.

We conclude that left ventricular aneurysmectomy performed in association with coronary artery bypass grafting confers no measurable improvement in overall resting ejection fraction as judged by radionuclide ventriculography. It is possible that global ejection fraction is not an appropriate measure of ventricular function in this group of patients and that more sensitive indices of wall motion abnormalities may show improvement, thus corroborating the clinical opinion that aneurysmectomy is of value.

Dr Crossland died recently.

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Prevalence of overt dilated cardiomyopathy in two regions of England

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SUMMARY The prevalence of dilated cardiomyopathy was assessed in two regions in England from 420 replies to 771 questionnaires sent to general practitioners. Overall point prevalence was 8.317 per 100 000 population in areas covering a total sample of 913 836 inhabitants. There was a statistically significant regional variation between East Anglia (Norfolk, Suffolk, and Cambridgeshire) and Essex, Hertfordshire, and Bedfordshire.

Though the natural history of dilated cardiomyopathy remains to be defined, this study has provided an assessment of point prevalence of overt cases of this condition.

Dilated cardiomyopathy belongs to the group of diseases defined as heart muscle diseases of unknown cause.¹ Studies of dilated cardiomyopathy have been beset by many problems in the past including the large number of synonyms under which this condition has masqueraded.² Clinical recognition and definition of the natural history are still not fully established.^{3,4} The reason for this is that myocardial hypertrophy and dilatation may be symptomless, and even when symptoms become manifest other diagnoses, which include that of ischaemic heart disease, may be ascribed to patients with this condition unless invasive and non-invasive investigations are undertaken.

Examination of endomyocardial biopsy tissue obtained by biopsome^{5,6} has contributed greatly to defining an infectious-immune mechanism for some patients with dilated cardiomyopathy⁷ so that a better understanding of the natural history is slowly emerging.

With the exception of two studies from the same centre in Sweden^{8,9} the prevalence of dilated cardiomyopathy is unknown. Numerous reports of often large numbers of cases from various centres have been published over the years,^{10,11} but these often act as reference centres, precluding therefore an assessment of prevalence. The purpose of this inquiry, which has hitherto not been undertaken in this country, was to establish an estimate of the prevalence of this condi-

tion. Furthermore, it was considered relevant to undertake this inquiry at this stage in view of the increasing number of patients with dilated cardiomyopathy being considered for transplantation.

Patients and methods

In the winter months of 1983-84 questionnaires were sent to general practitioners who were fellows, members, or associates of the Royal College of General Practitioners and resident in Norfolk, Suffolk, Cambridgeshire, Essex, Bedfordshire, and Hertfordshire. The questionnaire explained the need for information on the prevalence of dilated cardiomyopathy and Table 1 gives an example of the questions asked. An additional letter was sent stressing that only patients with dilated (congestive) cardiomyopathy according to the definition that excludes those patients who suffered from heart failure due to alcohol abuse or occurring in pregnancy or the puerperium or who had other known factors that could account for the symptoms were included. The total populations on the doctors' lists could be provided easily as they are regularly calculated by the local Family Practitioners Committee of the National Health Service. Furthermore we permitted respondents to reply on behalf of the group practice since in this way the scope of the inquiry could be considerably widened. In a few instances where the response was equivocal about where the diagnosis was made, a further letter was sent stressing the importance of the definitive diagnosis after reliable investigations. Only on receipt of a satisfactory reply were these cases included in the study.

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Accepted for publication 22 March 1985

Table 1 *Questionnaire sent to general practitioners*

How many patients do you have with dilated (congestive) cardiomyopathy on the date of receipt of this enquiry?		Please answer below
On my own list		
My list size is approximately		
On the practice list		
Practice list size		
How confident are you that a patient is not unknown to you?		
On your list		Fairly confident/Not confident
On practice list		Fairly confident/Not confident
		(please delete as applicable)
In <i>either case</i> do still return the form.		
If possible, where was the patient diagnosed?		
Approximately when?		

STATISTICAL ANALYSIS

The statistical test applied was the χ^2 test of independence (prevalence against area) significant at the 0.995 level.

Of the 771 questionnaires sent, 420 replies were received, which was considered acceptable. Some practitioners had retired or were engaged in other areas of primary care and did not possess a personal list of patients.

Results

Table 2 summarises the results.

Discussion

This study has provided an insight into the prevalence of symptomatic patients with this disease. The World Health Organisation (WHO)/International Society and Federation of Cardiology (ISFC) Task Force recommendations on definition and classification based on the original concepts of Goodwin and his colleagues were strictly followed. As has already been stated, cardiomyopathies are defined as "heart muscle diseases of unknown cause" and classified into dilated (congestive), hypertrophic, and restrictive forms.¹ To minimise confusion the term "specific heart muscle disease" was introduced and included all those cases with known secondary involvement of the heart due to metabolic diseases, including those due to deficiency, general systemic diseases, hereditary/familial neuromuscular diseases, and sensitivity and toxic reactions, among which alcohol was listed. Heart fail-

ure in peripartur heart disease was excluded according to the definition.

Since the natural history of dilated cardiomyopathy has not yet been fully established,⁴ and the fact that symptoms may not be manifest despite severely depressed left ventricular function, the cases included in this study represent only the tip of the iceberg of the true incidence of dilated cardiomyopathy.¹² Studies of patients with cardiomegaly or left bundle branch block in asymptomatic individuals undergoing medical check ups were also considered unhelpful for assessing the incidence of this condition. There is no evidence that asymptomatic subjects with a fascicular block develop dilated cardiomyopathy in later life. When cardiomegaly is evident on chest radiographs the condition is usually well advanced. Alternatively, despite evidence of left ventricular dilatation or malfunction by other investigations, cardiomegaly may not be evident on chest radiographs.¹² When these various factors are considered together with the fact that patients may be asymptomatic despite depressed left ventricular function being accidentally discovered it is evident that the true prevalence of dilated cardiomyopathy may be far greater. Our results therefore represent overt disease in patients who, as a result of their symptoms, presented to their doctor.

The only other study attempting to give an assessment of the incidence of dilated cardiomyopathy was undertaken by Torp in Malmö, Sweden, who during a period of eight years reported an incidence of 3/100 000 per year of the hospital population for a city of 250 000 inhabitants. If postmortem studies were included during the same period, however, the

Table 2 *Details of results from 420 replies to 771 questionnaires sent to general practitioners*

	No of cases of dilated cardiomyopathy	Patient population	Point prevalence (per 100 000)*
East Anglia (Norfolk, Suffolk, Cambridgeshire)	52	384 220	13.534
Essex, Hertfordshire, and Bedfordshire	24	529 616	4.532
Total	76	913 836	8.317

* χ^2 test of independence (prevalence against area) $p < 0.05$.

incidence rose to 5/100 000 patients per year.⁸ In a subsequent extended study an incidence of 7.5 cases was found with an estimate that 10/100 000 patients might be affected.⁹

Our overall figures of 8.317 cases per 100 000 population is in keeping with these results. Existing evidence points to a poor overall prognosis in symptomatic patients,¹⁰ so that prevalence figures would not be many times greater than those for incidence. It must also be remembered that Torp's study represented a sustained effort in one centre to remain vigilant for this particular diagnosis.

The variation in the prevalence between East Anglia (Norfolk, Suffolk, and Cambridgeshire) and Essex, Hertfordshire, and Bedfordshire is statistically significant ($p < 0.05$) and represents the first indication of an uneven geographical distribution of cases.

The reason for limiting the mailing of questionnaires to fellows, members, or associates of the Royal College of General Practitioners was the belief that these practitioners would co-operate in this study and would be more likely to be in possession of accurate medical records. In addition, a disease-index register was also more likely to have been maintained.

General practitioners are in the favourable position in that after initial appraisal and subsequent specialist investigation and diagnosis they have continued supervision of the patient. Even when the patient presented initially in hospital the practitioner would subsequently be fully informed by the specialist. It could be argued that a patient normally on the doctor's list might have presented to or continued under the care of a partner and therefore would be unknown to the respondent. This factor would of course also operate in the reverse direction and therefore should not materially affect the overall number of cases. Furthermore, many practitioners replied as units, and some were in the possession of detailed diagnostic registers.

Positive replies gave the name of the hospital where the diagnosis had been established after investigation. Often additional information was volunteered and respondents were well aware, in the additional information provided, of the distinction made between idiopathic dilated cardiomyopathy and cases secondary to pregnancy, alcoholic excess, or other factors contributing to heart failure. If in the initial reply any queries were raised about the accuracy of the diagnosis of dilated cardiomyopathy, or whether a history of alcohol intake or pregnancy could possibly be pathogenetically linked to the heart failure, the practitioner was asked for additional information to eliminate any mistaken inclusion of these patients. Only patients with dilated cardiomyopathy, as defined,¹

were included in the study.

This preliminary study has therefore provided an assessment of the prevalence of overt dilated cardiomyopathy. Clearly, other regions and a greater number of the population must now be investigated. We hope that this report will act as a catalyst for others to undertake similar studies.

We thank Dr G Janacek, University of East Anglia, for statistical advice, and the Royal College of General Practitioners for their help.

This study was undertaken as part of the Multicentre Research study on dilated cardiomyopathy of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology.

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Familial right ventricular dilated cardiomyopathy

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SUMMARY Cardiomyopathy of unknown cause occurred in three of six siblings. The course of the illness was marked by life threatening supraventricular and ventricular arrhythmias, sinoatrial block, atrioventricular block, and embolism (in one patient). The disease was characterised by right ventricular dilatation. Two of the three patients died aged 32 and 48.

No new cases of the disease were found when a further 33 family members from three generations were investigated.

Dilated cardiomyopathy¹ is characterised by dilatation of the left or right ventricle or both and an increase in the weight of the heart. Patients with dilated cardiomyopathy may have atrial or ventricular arrhythmias and heart failure due to impaired systolic left and right ventricular function, and they often die at an early age. There are several published reports of the familial occurrence of dilated cardiomyopathy.²⁻⁵ In 1981, Fitchett *et al* described a type of dilated cardiomyopathy in which right ventricular involvement was most pronounced.⁶

We report three cases of dilated cardiomyopathy that occurred in a family of six siblings. Two died prematurely, one of them before our investigations were completed; necropsy was not performed. To elucidate a possible hereditary cause of the condition we investigated a further 33 family members in three generations.

Patients and methods

All eligible living family members underwent physical examination, radiography of the chest, and electrocardiography. The histories of those who had died were derived from case records or were supplied by the family. Initially we investigated only the parents, siblings, and children of siblings of the patients, but the study was extended to siblings of the mother because of reports of unidentified heart disease in three other members of her family. The father's sib-

lings and their families were not investigated because there was no evidence from the family to suggest other cases of heart disease among his relatives.

CASE 1

This woman was the third child in a family of six siblings. She was a moderate drinker and smoked about 10 cigarettes a day. She had experienced dyspnoea on exertion since the age of 26. Eight years later she was awarded a disability pension because of dyspnoea, and at the age of 37 she had heart disease classified as New York Heart Association functional class III.

Her heart had been dilated since the age of 29, and four years later she was given digitalis for intermittent atrial fibrillation. Before digitalisation the electrocardiogram showed flattened T waves in all leads, and this was a constant finding throughout her illness. At the age of 42, right sided heart decompensation was demonstrated for the first time, and quinidine was prescribed for ventricular extrasystoles.

Two years later she had ventricular tachycardia with subsequent cardiac arrest despite treatment with quinidine. Two days after drug treatment had been stopped there was still intermittent ventricular tachycardia and cardiac arrest alternating with third degree atrioventricular block, and for this reason a pacemaker (CPI-Minilith P) was implanted. Other findings are given in the Table.

At the ages of 33 and 44 the patient had transient pulmonary infiltrates of undetermined cause. She died in hospital at the age of 48 years after an episode of ventricular fibrillation. Shortly before death she had two episodes of right sided hemiparesis.

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Accepted for publication 2 April 1985

Table Data on cases 1 and 2

	Case 1 (F)			Case 2 (M)
	29	34	47	31
Blood pressure (mm Hg)			125/80	110/70
Auscultation			Normal	Normal
Weight (kg)	60			73
Height (cm)	153			173
Cardiothoracic ratio (cm)	14/27		19/26	17.5/33
Echocardiography and angiocardiography			Dilated RV and RA, LV volume normal with good contractility	Dilated RV and RA, LV volume normal but decreased contractility
LV catheterisation				Normal
RV catheterisation:				
Cardiac output (l/min)	Rest 3.6	Exercise 4.1		2.6
		8.4†	7.4*	4.9†
Pulmonary wedge pressure (mmHg)	Rest 15/10-12	Exercise 16/10-15		12
		24/14†	26/18*	12‡
Pulmonary arterial pressure (mmHg)	Rest 21/14-19	Exercise 29/14-22		26/11-17
		35/20‡	34/21*	30/11-14‡

RV, right ventricle; RA, right atrium; LV, left ventricle.

*25 W for 3 minutes; †50 W for 5 minutes; ‡100 W for 5 minutes.

PATHOLOGICAL FINDINGS

The heart was enlarged and globoid, weighing 490 g (0.8% of body weight). The right side was grossly dilated (Fig. a, b, c). The left atrium was also slightly dilated, but the left ventricular cavity size appeared to be normal. There were no congenital abnormalities.

The cusps were normal, but the tricuspid ostium was dilated (132 mm; mitral ostium 108 mm). The endocardium of the right ventricular cavity was patchily thickened by fibrosis; there were no parietal thrombi, either in this cavity or on the left side. The tip of the pacemaker electrode was encased in endocardial fibrotic tissue posteromedially at the base of the right ventricle. The myocardium was pale with slightly increased fibrosis on the cut surface. There were no signs of recent or old infarction, and the coronary arteries were normal without atherosclerosis.

There were old small infarcts in the left hemisphere of the brain, both kidneys, and the spleen, although no parietal thrombi or their sequelae were seen in the left ventricle. Apart from slight chronic congestion the lungs were normal and there was no evidence of thromboembolism.

Sections from the right ventricle showed hypertrophy with fibre attenuation, fibrosis of the replacement type, and fatty infiltration. There was some diffuse infiltration of lymphocytes in the right atrium caused by implantation of the pacemaker electrode. The myocardium of the left ventricle showed similar but less pronounced changes.

Only the atrioventricular area of the conduction system was available for investigation (the top of the right atrium had been cut off at initial necropsy). Slight nonspecific fibrosis was seen in the bundle of

His and in the left main fascicle. There were no granulomas or inflammatory cell infiltration.

CASE 2

This 36 year old man was a brother of case 1. He was the youngest of six siblings. He was a moderate drinker and he smoked 10 cigarettes a day.

He had completed his military service without difficulty at the age of 20. He had experienced dyspnoea on exertion since the age of 31 years, and because of cardiomyopathy he was awarded a disability pension when he was 34 years old. At that time he had heart disease classified as New York Heart Association functional class III.

Since the age of 31 he had been treated with digoxin because of atrial flutter. Before digoxin treatment the electrocardiogram showed atrial flutter with 3:1 block, incomplete right sided bundle branch block, and a negative T wave in V2-V5. During exercise testing the His bundle electrocardiogram showed that two out of three impulses were blocked at the atrioventricular junction, and during exercise at 50 W for five minutes he developed 2:1 block. With additional exercise of up to 100 W 1:1 block developed with a heart rate of 264 beats/minute. Because the heart rate did not fall after exercise had stopped DC cardioversion was given. Atrial flutter recurred a few days later despite quinidine treatment. Further findings are given in the Table.

CASE 3

This patient was the brother of cases 1 and 2. He was the fourth of six siblings. He drank very little alcohol and smoked few cigarettes.

He had completed military service without

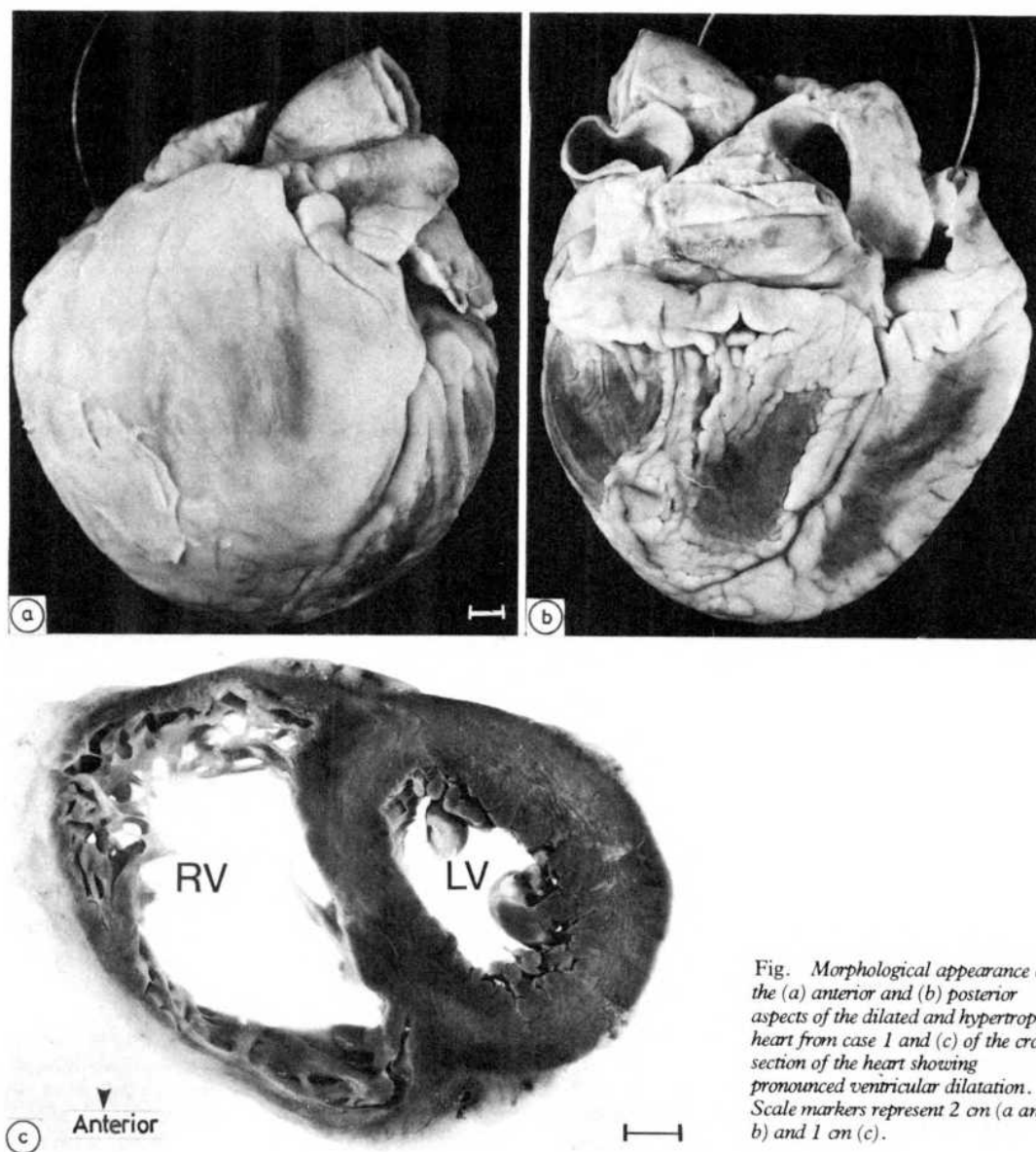


Fig. Morphological appearance of the (a) anterior and (b) posterior aspects of the dilated and hypertrophic heart from case 1 and (c) of the cross section of the heart showing pronounced ventricular dilatation. Scale markers represent 2 cm (a and b) and 1 cm (c).

difficulty. At the age of 24 he began to experience dyspnoea on exertion and stress induced palpitation. He was awarded a disability pension at the age of 30 because of heart disease (New York Heart Association functional class III).

During hospital admission at the age of 26 no decompensation of the heart was demonstrated. Cardiac auscultation was normal. Blood pressure was 120/80 mm Hg. Before medical treatment an electrocardiogram showed alternating sinus rhythm and

atrial flutter, with varying degrees of atrioventricular block; there were negative T waves in leads V2-V3. Radiography of the heart and lungs showed a cardiothoracic ratio of 0.59.

He was found dead in bed at the age of 32 years. Necropsy was not done.

OTHER FAMILY MEMBERS

Three other members of the family (all on the maternal side), who had died many years before our study,

were reported to have had heart disease. Data on them were incomplete and too unreliable for a diagnosis of cardiomyopathy. Three siblings, children of one of the patients' healthy siblings had electrocardiographic changes in V1. No other signs of cardiac disease were found in the 33 family members examined.

Discussion

There are other published reports of the occurrence of familial dilated cardiomyopathy.²⁻⁵ We believe that the three siblings we describe had the same cardiac disease, although the data in case 3 are limited because the patient died 16 years ago. No other cases of dilated cardiomyopathy have been found in the family.

Examinations carried out in cases 1 and 2 excluded diseases such as ischaemic, valvar, and congenital heart disease. Furthermore, it was not possible to demonstrate specific cardiac muscle disease or signs of pulmonary disease. A shared (unknown) environmental cause seems unlikely. The siblings did not live close to each other and there was an interval of 17 years between the appearance of the disease in the youngest patient (case 2) and manifestation in the oldest patient (case 1).

The symptoms, irregular palpitation of the heart and dyspnoea on exertion, started between the ages of 25 and 30 years. Two patients died at the ages of 32 and 48 years.

Although case 1 had had symptoms typical of left heart disease for many years, echocardiography and necropsy demonstrated mainly changes of the right side of the heart. Both right atrium and right ventricle were dilated, while the left atrium and ventricle were of normal size; similarly in patient 2 the right side of the heart was enlarged, although to a lesser degree.

Fitchett *et al* and Rowland *et al* described cases of dilated cardiomyopathy with predominantly right ventricular dilatation.⁶⁻⁸ The disease presented clinically as either right heart failure or arrhythmias and syncope. Our patients had arrhythmias, which were the cause of death in case 1 and probably also in case

3. In case 1 right heart failure was a late event. Unlike the patients investigated by Fitchett *et al* and Rowland *et al*, however, our patients had clinical signs of involvement of the left side of the heart. At necropsy there was gross and histological evidence for involvement of both sides of the heart in three of Fitchett's patients. We believe that our investigation adds further support to the concept of right ventricular dilated cardiomyopathy, which in our opinion represents one end of the spectrum of dilated cardiomyopathy rather than an independent type of (familial) cardiomyopathy.

We thank Dr Per Henningsen for echocardiographic guidance.

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Plasma free captopril concentrations during short and long term treatment with oral captopril for heart failure

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SUMMARY Plasma free captopril concentrations and haemodynamic response to captopril were studied in 20 patients with severe chronic heart failure. A 25 mg oral dose of captopril produced a 36% reduction in systemic vascular resistance, with individual responses varying from 13% to 64%. Mean systemic pressure fell by 20% and cardiac output rose 28%. The absorption of captopril was rapid. Peak plasma free captopril concentration occurred at 45 minutes after the dose and was followed by a smaller second peak. Peak plasma free captopril concentrations varied more than 20-fold but did not correlate with the maximal reduction in systemic vascular resistance. Elimination half life was seven hours. Fourteen patients were restudied after 1-2 months of captopril treatment and 12 showed symptomatic benefit. There was a sustained improvement in haemodynamic state and in non-invasive indices of myocardial function. During long term treatment the predose plasma free captopril concentration correlated well with dosage, but steady state captopril concentrations did not show a significant relation with haemodynamic response. On a dosage regimen of 25-50 mg three times daily the morning predose plasma free captopril concentration and plasma renin activity were relatively low and suggested that maximal inhibition of the renin-angiotensin system was not maintained throughout the dosage interval.

Captopril, a vasodilator which acts by inhibiting conversion of angiotensin I to angiotensin II, has been shown to benefit patients with chronic severe heart failure.¹ The response to captopril varies appreciably between subjects, but the reasons for this are not fully understood. Measurement of plasma concentrations of captopril has been difficult because of the highly reactive thiol group in the captopril molecule. A radioimmunoassay for captopril has been developed,² using antibodies to a captopril-*N*-ethylmaleimide complex, and we have used this assay to study the relation between plasma free captopril concentrations, haemodynamic responses, and plasma renin activity.

Patients and methods

STUDY POPULATION

Twenty patients (mean age 62.4 (range 47-71) years) were studied, all of whom had severe left ventricular

myocardial impairment due to ischaemic heart disease in 13 and cardiomyopathy in seven. Nine had an associated valve abnormality and three mild hypertension. Each patient had continued to have cardiac symptoms at rest or with mild activity despite treatment with digoxin and frusemide (mean dose 188 (range 80-500) mg/day). All patients were taking a diet without added salt. Potassium supplements (seven patients) and potassium retaining agents (13 patients) were withdrawn when captopril treatment began.

SHORT TERM RESPONSE

Each patient was given an initial dose of 25 mg captopril dissolved in 150 ml water. Haemodynamic measurements were made at 30, 15, and 0 minutes before this dose and for four hours (10 patients) or 1½ hours (10 patients) thereafter. Patients remained supine throughout the study period and for at least one hour before control recordings. They had fasted overnight and had not taken other medications on the day of study. A balloon flow directed catheter was used to record right atrial and pulmonary artery pres-

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Accepted for publication 19 March 1985

tures and the cardiac output. Cardiac output was measured by indicator dye dilution (eight patients) or thermodilution (12 patients). Systemic pressure was recorded with a sphygmomanometer and arm cuff. Changes for all haemodynamic variables were measured at the time of each individual's maximal change in systemic vascular resistance.

LONG TERM RESPONSE

Patients were restudied at 1–2 months after beginning captopril treatment. Dosage had been adjusted until symptomatic hypotension occurred or until a maximum dosage of 450 mg/day (12 patients) or 150 mg/day (eight patients) was reached. Haemodynamic measurements, plasma free captopril concentrations, and plasma renin activity were recorded at three intervals over 30 minutes as in the control period described above. The last captopril dose was given 4–6 hours before the repeat study.

Left ventricular function was assessed by nuclear ventriculography and echocardiography before captopril treatment and at repeat study 1–2 months later. Patients underwent exercise testing on a treadmill using the Bruce protocol modified to include an initial lower stage of 1.5 kph at an 8° incline: a practice run had been given.

ASSAY OF PLASMA FREE CAPTOPRIL CONCENTRATION

For the radioimmunoassay of captopril 10 mg *N*-ethylmaleimide was added to 5 ml plasma separated in a refrigerated centrifuge immediately after withdrawal of the blood sample. The radioimmunoassay technique has been described elsewhere.² The sensitivity of the assay is 2 ng/ml and the interassay coefficient of variance is 7.5%.

PLASMA RENIN ACTIVITY

Plasma renin activity was measured using the technique of Drury and Edwards.³ The range for normal supine subjects is 0.3–1.5 ng/ml/h. The coefficients of variance were 10% (intra-assay) and 18% (interassay).

Results

SHORT TERM RESPONSE

Haemodynamic response—Table 1 shows haemodynamic changes found after the first 25 mg dose of captopril. Systemic vascular resistance fell by 36% to reach a mean level just above the upper limit of the normal range. The percentage reduction in systemic vascular resistance for individual subjects ranged from 13% to 64%.

Plasma free captopril—Captopril was absorbed rapidly with the peak concentration at 45 minutes after the dose. The rise in plasma free captopril coincided with the fall in systemic vascular resistance and was followed closely by an increase in plasma renin activity. Figure 1 shows the time profiles of changes in systemic vascular resistance, plasma free captopril concentration, and plasma renin activity in 10 patients. The areas under the four hour free captopril absorption curves varied from 44 to 689 mg/ml/h (mean (SD) 352(237)).

Peak plasma free captopril concentrations varied appreciably, but there was no significant correlation (Fig. 2) between the maximal percentage reduction in systemic vascular resistance and the peak plasma free captopril concentration ($r=0.28$) or its log concentration ($r=0.40$).

A small second peak of plasma free captopril concentration was seen in 16 of the 18 patients who had plasma free captopril concentrations measured up to four or 24 hours after the dose. The mean secondary rise was 38.1 mg/ml from a mean preceding concentration of 56.3 mg/ml. Of the eight subjects in whom plasma free captopril was measured for 24 hours, two had slow absorption with peak captopril concentrations at 90 and 240 minutes after the dose. The other six patients showed a rapid absorption of captopril (peak concentration <60 minutes after the dose); a small second peak was apparent at two hours in these subjects (Fig. 3). The elimination rate of free captopril, measured from five to 24 hours after the dose in these six subjects, was seven hours.

Table 1 Short term haemodynamic response to 25 mg oral captopril in 20 patients. Values are mean (SD) unless stated otherwise

	Before captopril p	After initial 25 mg oral dose	% Change	p value (paired t test)
Systemic vascular resistance (dyn s cm ⁻⁵)	2350 (788)	1503 (693)	-36.0	<0.001
Mean systemic pressure (mm Hg)	91.3 (14.2)	73.3 (14.7)	-19.7	<0.001
Cardiac output (l/min)	2.80 (0.58)	3.57 (0.81)	+27.5	<0.001
Pulmonary end diastolic pressure (mm Hg)	30.5 (7.3)	25.1 (6.8)	-17.7	<0.001
Mean right atrial pressure (mm Hg)	13.2 (4.4)	11.4 (4.2)	-13.6	<0.01
Heart rate (beats/min)	75.7 (10.4)	75.5 (12.5)	-0.3	NS
Plasma renin activity (ng/ml/h)	5.70 (6.23)	34.58 (33.21)	+506.6	<0.001

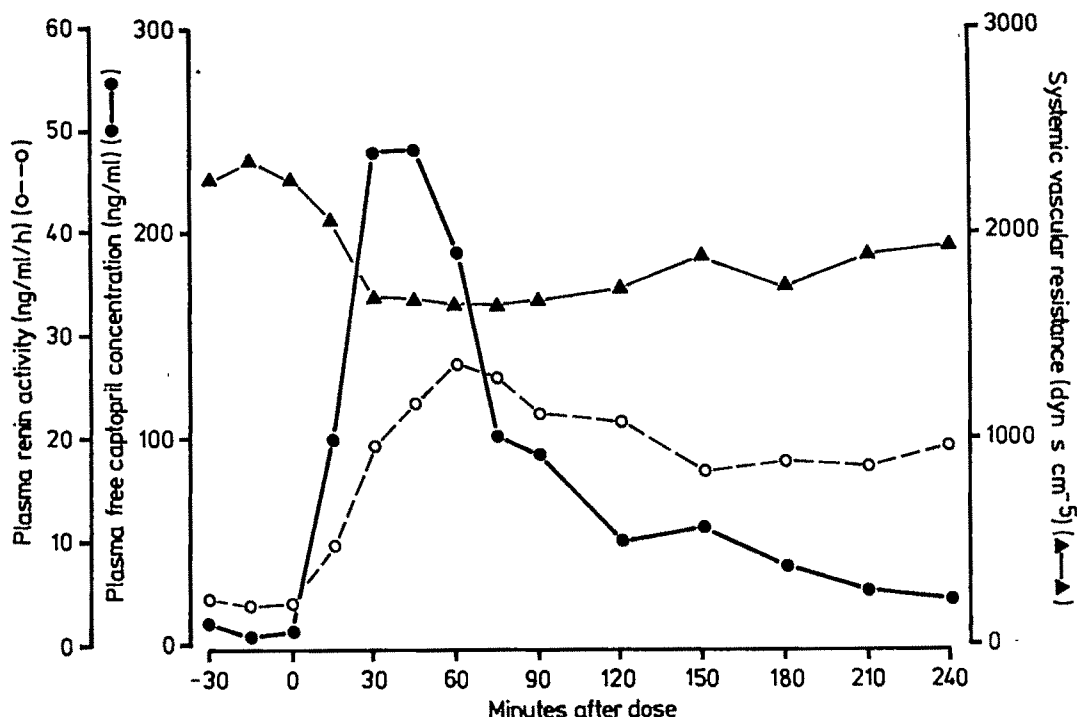


Fig. 1 Mean plasma free captopril concentration (●), systemic vascular resistance (▲), and plasma renin activity (○) measured before and for four hours after a 25 mg oral dose of captopril ($n = 10$).

LONG TERM RESPONSE

Four patients, all of whom had control plasma renin activity > 10 ng/ml/h, did not tolerate captopril treat-

ment, three because of lightheadedness or syncope and one because of taste disturbance. One patient with three vessel coronary artery disease died suddenly after 17 days of captopril treatment. A further patient, who had mitral stenosis and myocardial impairment, showed progressive deterioration: he died nine days after captopril treatment ended. Fourteen patients were therefore available for repeat study. Twelve of these patient showed symptomatic improvement with captopril treatment (Fig. 4).

Haemodynamic response—Table 2 summarises the haemodynamic and non-invasive variables before and after 1–2 months of captopril treatment.

Plasma free captopril—The dosage of captopril at repeat study ranged from 75 mg/day to 450 mg/day. The mean plasma concentrations for daily dosages of 75 ($n=4$), 150 ($n=7$), and 300–450 mg ($n=3$) were 46, 73, and 233 ng/ml respectively. There was a significant correlation between dosage and free captopril concentration ($r=0.77$, $p<0.01$).

As with the short term response, no correlation existed between percentage reduction in systemic vascular resistance and plasma free captopril concentration ($r=0.09$).

Plasma free captopril concentration and plasma

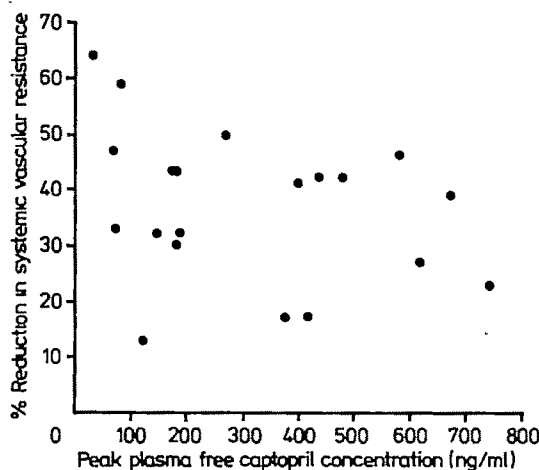


Fig. 2 Relation between percentage reduction in systemic vascular resistance and peak plasma free captopril concentration in 20 patients with severe chronic heart failure.

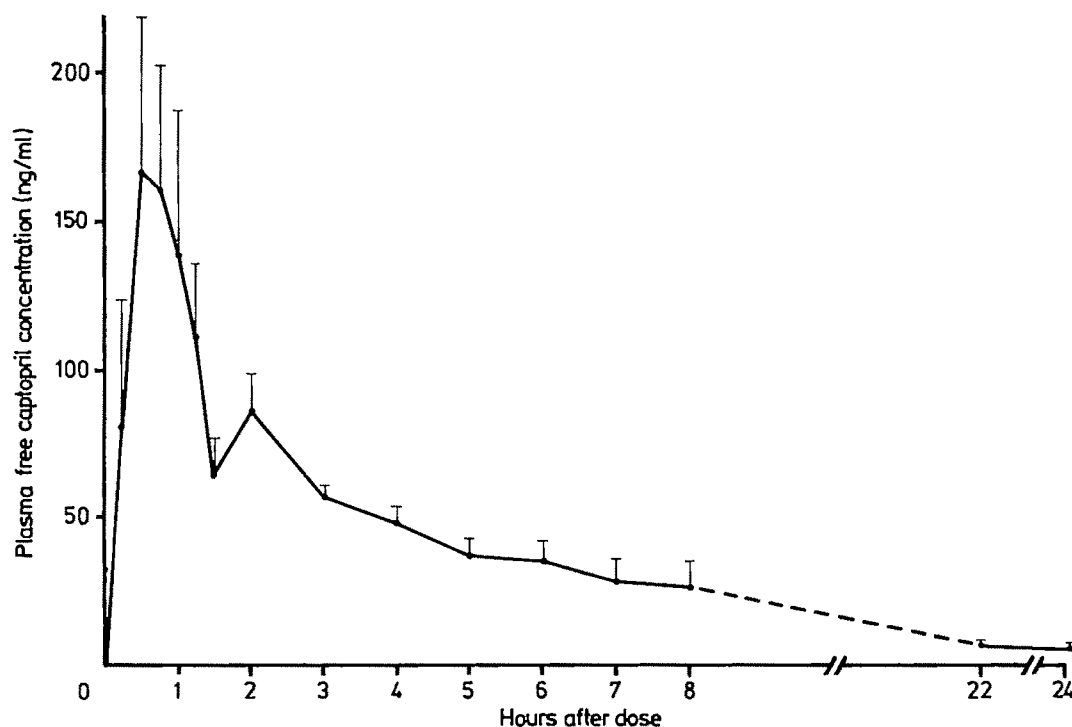


Fig. 3 Mean (SEM) plasma free captopril concentrations during 24 hours after a 25 mg oral dose of captopril in six patients who showed rapid absorption (peak plasma free captopril ≤ 60 minutes).

renin activity were measured throughout an eight hour dose interval during long term treatment in six patients. Two were receiving 25 mg three times daily and four 50 mg three times daily. Figure 5 shows the results. The predose (0900 h) plasma free captopril concentration was low, and there was a pronounced rise in drug concentration after absorption of the dose, with a small second peak at six hours. Plasma renin activity showed a further increase after the dose.

Discussion

In individual cardiac patients the haemodynamic and symptomatic response to captopril can vary from minimal to very substantial. Our results, like other studies,^{1,4,5} show an overall moderate degree of improvement in symptoms, resting haemodynamic indices, and non-invasive indices of cardiac function, and they confirm the wide range of individual responses. Since this was an open study and a placebo period was not included the changes in symptom status have to be interpreted with caution. Similar benefits from captopril in heart failure have, however, been found in double blind controlled studies.⁶⁻⁸

Wide differences in peak plasma free captopril concentration were found but did not correlate with

maximal percentage change in systemic vascular resistance. Plasma also contains captopril linked to the plasma proteins, cysteine and glutathione, and captopril molecules linked together as disulphide bond dimers,^{9,10} but these compounds are not thought to be biologically active. The lack of relation between maximal response and peak plasma free captopril concentration after a 25 mg oral dose may be explained by the flat dose-response relation found in incremental dose studies when captopril dose exceeded 6.25 mg. There was also no correlation between captopril concentration and long term response, and our results do not show any evidence that measurement of plasma free captopril concentration would be useful in monitoring response.

The early peak concentrations of plasma free captopril indicate that absorption of captopril occurred rapidly in the fasting patients in this study. This coincided with a rapid onset of action. The pronounced variation in the peak plasma free captopril concentrations and in the area under the four hour curves could arise from several factors including impairment of the extent of absorption due to the presence of cardiac failure, degradation or binding of captopril within the gastrointestinal tract, differential metabolism, or differences in the volume of drug distribution. McKins-

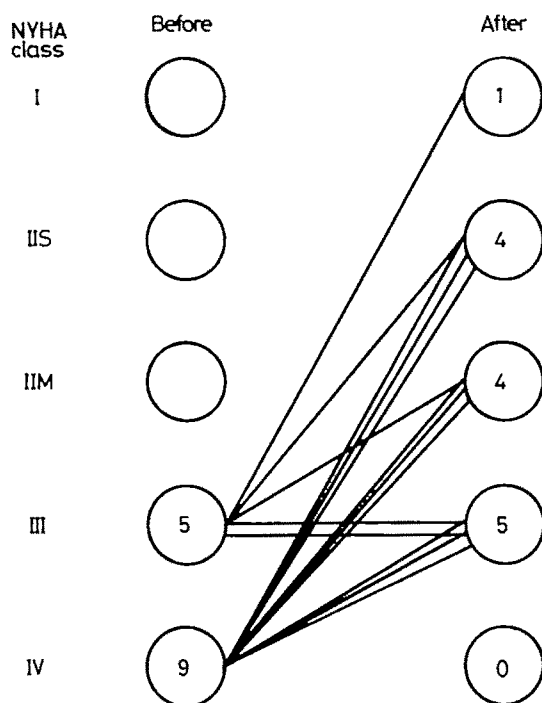


Fig. 4 Symptom status (NYHA class) in the 14 patients before and after long term treatment with captopril.

try *et al* gave oral doses of isotopically labelled captopril to normal subjects and estimated total absorption to be 68% (SD 9%), but in the first few hours after the dose less than half of the total plasma radioactivity was associated with free captopril and there was extensive conversion to the inactive forms.¹¹ Cody *et al* also found that the concentration of bound captopril was higher than the concentration of free captopril during 0–8 hours after an oral dose.¹² They suggested that the bound forms might constitute a reservoir for the active drug.

A small second peak in the absorption curve was

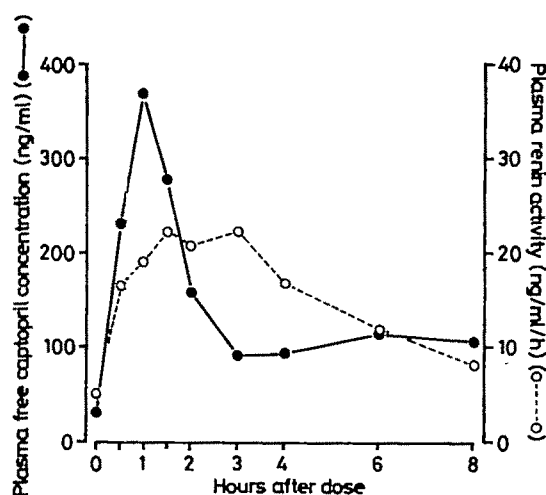


Fig. 5 Mean plasma free captopril concentrations (●) and plasma renin activity (○) in six patients studied during a dosage interval while receiving long term treatment with captopril.

found in most of our patients. This may be due to enterohepatic recirculation. This second peak was not large and was associated with only a small and statistically insignificant secondary decrease in systemic vascular resistance at 180 minutes after the dose (Fig. 1). Levine *et al* also observed a small secondary peak in response.¹³ The true elimination rate of a drug is often difficult to establish as the absorption and distribution phases can continue until the plasma drug concentration is too low for the sensitivity of the assay. This second peak complicates the estimation of the elimination rate of plasma free captopril, but when taken between 5 and 24 hours after the dose we found the log concentration time plot to be linear and the elimination half life to be seven hours.

We found that throughout an eight hour dose interval during long term treatment (25–50 mg three times daily) the plasma free captopril concentration was maintained at levels which had provided some

Table 2 Long term response to captopril treatment in 14 patients. Values are mean (SD) unless stated otherwise

	Before captopril p	After 1–2 months' treatment	% Change	p value (paired t test)
Systemic vascular resistance (dyn s cm ⁻⁵)	2397 (768)	1926 (635)	-19.6	<0.001
Mean systemic pressure (mm Hg)	92.7 (14.8)	88.7 (10.8)	-4.3	NS
Cardiac output (l/min)	2.88 (0.61)	3.49 (0.80)	+21.2	<0.01
Pulmonary end diastolic pressure (mm Hg)	30.1 (6.3)	24.4 (5.5)	+18.9	<0.02
Mean right atrial pressure (mm Hg)	11.8 (3.3)	9.6 (3.5)	-18.6	NS
Heart rate (beats/min)	76.6 (9.3)	72.3 (9.5)	-5.6	NS
Plasma renin activity (ng/ml/h)	2.6 (2.9)	8.3 (4.3)	+219 (n=11)	<0.01
Exercise duration (min)	2.64 (3.03)	4.48 (3.26)	+70	<0.02
Echocardiographic fractional shortening (%)	10.8 (3.6)	14.0 (3.8)	+30	<0.01
Nuclear ejection fraction (%)	24.1 (7.0)	34.0 (11.3)	+41 (n=10)	<0.05

haemodynamic response in the acute study. Plasma renin activity remained increased but showed a further increase after the dose. This suggests that a thrice daily dosage schedule is adequate for maintaining a haemodynamic response but possibly not at a maximal level throughout the eight hour period at this dosage. Larger doses of captopril are, however, associated with a greater incidence of side effects, and for this reason dosages of >150 mg/day are now seldom used.

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Role of echocardiography in differential diagnosis of broad complex tachycardia

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SUMMARY It is not always easy to distinguish between supraventricular tachycardia with aberration and ventricular tachycardia by electrocardiographic analysis alone. M mode echocardiography can often help by providing direct or indirect evidence of the relation between atrial and ventricular contraction. Sixteen consecutive patients with spontaneous sustained broad QRS complex tachycardia with heart rates of 120-225 beats/minute were examined. Echocardiographic evidence of 1:1 conduction was seen in three cases and 2:1 atrioventricular conduction in one (all four had supraventricular tachycardia, confirmed by intracardiac electrocardiography in three). Evidence of retrograde block was seen in 12 (all had ventricular tachycardia, with electrophysiological confirmation in 10). Satisfactory views of the mitral valve were obtained in all patients.

Patients with ventricular tachycardia had a variable mitral valve opening time (range 42-110%) compared with those who had supraventricular tachycardia (9-15%). Aortic root and left atrial views gave direct evidence of atrial contraction in three cases, and subcostal right atrial wall views were diagnostic in four of five cases. Seven patients with ventricular tachycardia had been wrongly diagnosed elsewhere as having supraventricular tachycardia. This study confirms that echocardiography is a simple and rapid aid to accurate diagnosis in patients with broad QRS complex tachycardia.

It may be difficult to decide whether a broad complex tachycardia is supraventricular or ventricular in origin. Examination of the surface 12 lead electrocardiogram may provide an accurate diagnosis.^{1,2} Clinical examination may also be helpful³ if simultaneous observation of the jugular venous pulse and palpation of the arterial pulse show evidence of associated or dissociated atrial contraction.

When the diagnosis is in doubt after clinical examination and analysis of the electrocardiogram, the choice lies between assessing the response (physiological or pharmacological) to treatment and invasive investigation.

M mode echocardiography has been shown to be a useful investigation in this situation, mainly by providing non invasive evidence of atrioventricular association or dissociation.⁴⁻⁶ Various echocardiographic observations and variables have been suggested.^{4,6,7} We set out to examine which views, fea-

tures, and measurements would be useful in the diagnosis of broad complex tachycardias and to assess the technical problems of obtaining good quality recordings.

Patients and methods

All patients with regular broad complex tachycardias seen in a 16 month period in 1982-83 were eligible for the study whether or not the diagnosis was apparent from the initial electrocardiogram.

We studied 16 patients (12 male) aged 11-82 years. Thirteen had ischaemic heart disease, and in five the arrhythmia was associated with recent or acute infarction. Of the others, one had an ostium primum atrial septal defect, one hypertrophic cardiomyopathy, and one no identifiable heart disease.

Seven patients were referred from other hospitals after initial treatment of their arrhythmias had been unsuccessful. Nine patients had already had antiarrhythmic drugs by the time of examination, and in seven (including six referred patients) the initial treatment had been inappropriate because the correct diagnosis had not been made.

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Accepted for publication 29 April 1985

We set out to record parasternal M mode traces of the mitral valve and of the aortic valve and left atrium in all cases, and in the last five patients we also performed a subcostal examination. All M mode scans were derived from the sector scan.

Recordings good enough to establish the relation between atrial and ventricular contraction were obtained in all patients. Some patients in the group were poor subjects for echocardiographic examination and many were old or ill. Echocardiography is difficult in this situation, and if good quality recordings were not quickly available from all parts of the heart and in all views we did not persist with the examination because urgent treatment was often considered necessary. In two patients the episodes of arrhythmia ended spontaneously and the examination was incomplete.

All patients had a standard 12 lead electrocardiogram and a rhythm strip. The echocardiograms were recorded at 100 mm/s with a simultaneous electrocardiogram and were obtained with a Toshiba SSH-10A phased array scanner or an Advanced Technology Laboratories MK 300C mechanical scanner, both with 3 MHz probes. Where possible, 20 consecutive cycles of the mitral valve and the aortic valve were recorded. Manyari *et al* first described the pattern of movement of the mitral and aortic valves in supraventricular and ventricular tachycardia.⁴ In the light of their report we measured the following in our patients: cycle length; duration of mitral valve opening; and duration of aortic valve opening. The percentage variability of the mitral and aortic opening times was calculated as: $100 \times (\text{maximum} - \text{minimum value}) / \text{minimum value}$. In addition, the mitral valve, aortic valve, posterior aortic wall, left atrial posterior wall, and subcostal right atrial wall were examined for evidence of independent or associated atrial activity ("A" waves).

In four patients the diagnosis was made confidently from the electrocardiogram and the response to treatment. In two patients echocardiography was performed during subsequent electrophysiological stimulation of the same arrhythmias because they had been too ill on admission for inclusion in the study. Twelve patients underwent electrophysiological study, usually a limited procedure to confirm the diagnosis and to terminate the arrhythmia by means of programmed stimulation.

Results

Satisfactory views of the mitral valve were obtained in all patients. The aortic valve was seen well enough for measurement of the opening time in only four patients, and the posterior wall of the aorta provided diagnostic information in another two. The left atrial

posterior wall was seen clearly in eight patients, but in only one case were definite atrial contractions seen. Subcostal echocardiography was performed in the last five patients and good views of the right atrial wall were obtained in four. These results are summarised in the Table.

Twelve patients were found to have ventricular tachycardia with heart rates between 132 and 225 beats/min (mean (SD) 165 (25)). Eleven of the 12 had ischaemic heart disease. The diagnosis of ventricular tachycardia was confirmed by electrophysiological study in 10 cases. Of the 12 patients, 10 had evidence of ventriculoatrial dissociation and two had retrograde Wenckebach block. In two cases the admission electrocardiogram showed 2:1 ventriculoatrial conduction, but there was retrograde block by the time the echocardiogram was performed, the change in one case being in response to carotid sinus massage. No ventricular tachycardia with 1:1 retrograde conduction was seen.

Four patients had supraventricular tachycardia with heart rates of 120–190 beats/min (mean (SD) 158 (34)). There was 1:1 atrioventricular conduction in three, confirmed by electrophysiological study in two. The fourth patient had atrial flutter with 2:1 conduction. Two patients with supraventricular tachycardia had aberrant conduction during the tachycardia, and the other two had an underlying bundle branch block when they returned to sinus rhythm.

The echocardiogram correctly identified the relation between atrial and ventricular contraction in all patients, but in the case of 1:1 conduction it could not distinguish between anterograde and retrograde conduction. The variability of mitral opening times in ventricular tachycardia was 42–110% and in supraventricular tachycardia it was 9–15% (Fig. 1). Aortic valve opening time in ventricular tachycardia was 32%, 33%, and 54% in three cases and only one value was obtained in supraventricular tachycardia (16%).

Independent "A" waves on the anterior mitral valve leaflet have been described in ventricular tachycardia⁴ but were seen in only four cases in this series, probably because heart rates in our group were higher than those reported previously. "A" waves

Table Success rates of various echocardiographic views. Figures are numbers of patients

	Clearly seen	Diagnostic*
PS mitral valve	16/16†	16/16
PS aortic valve	4/16†	4/16
PS aortic wall	9/16	2/16
PS left atrial wall	8/16	1/16
SC right atrial wall	4/5	4/5

*Gave definite evidence of relation between atrial and ventricular contraction.

†Seen clearly enough for accurate measurement
PS, parasternal; SC, subcostal.

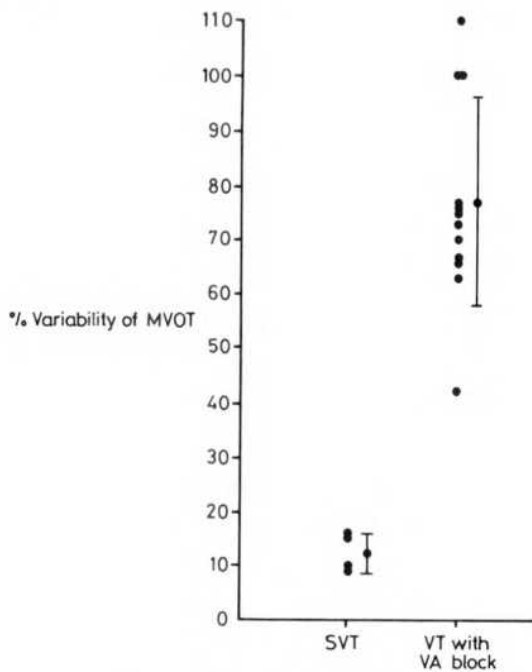


Fig. 1 Range of variability of mitral valve opening time (MVOT) in patients with supraventricular tachycardia (SVT) or ventricular tachycardia (VT) with ventriculoatrial (VA) block. Bars denote mean (1 SD).

were not seen on the aortic valve or left ventricular recordings in any patient.

Figure 2 shows the pronounced variability of mitral opening times seen in ventricular tachycardia, and this was easily distinguished from that seen in 1:1 conduction (Fig. 3). Mitral opening was also constant in 2:1 atrioventricular conduction. Figure 4 shows the variable aortic valve opening time seen in ventricular tachycardia, whereas aortic opening in supraventricular tachycardia is regular.

Evidence of dissociated atrial activity was occasionally seen on the posterior wall of the aorta in ventricular tachycardia and when present was diagnostic (Fig. 5). Echocardiography of the left atrial wall was generally disappointing as, even when it was seen clearly and there was other echocardiographic evidence of atrial contraction, "A" waves were not seen (Fig. 5).

Subcostal views were diagnostic in four patients. The recordings were taken from the right atrial wall just above the tricuspid valve ring with the M mode beam being positioned on the sector scan. It was apparent from examining both cross sectional and M mode recordings that movement transmitted from ventricular contraction produced low amplitude movement or vibration of the right atrial wall in time with the QRS complex on the electrocardiogram. Atrial contractions appeared as larger amplitude discrete posterior movements.

Subcostal examination showed ventricular tachycardia with retrograde block in one patient (Fig. 6) and ventricular tachycardia with retrograde Wenckebach conduction in another.⁸ A third patient had

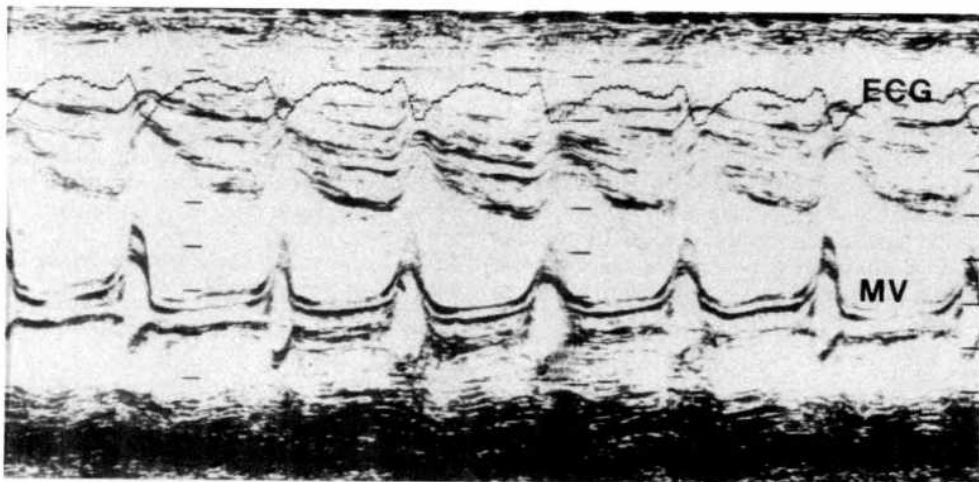


Fig. 2 Parasternal M mode echocardiographic view of the mitral valve (MV) in a patient with ventricular tachycardia. There is pronounced beat to beat variability of mitral opening time.

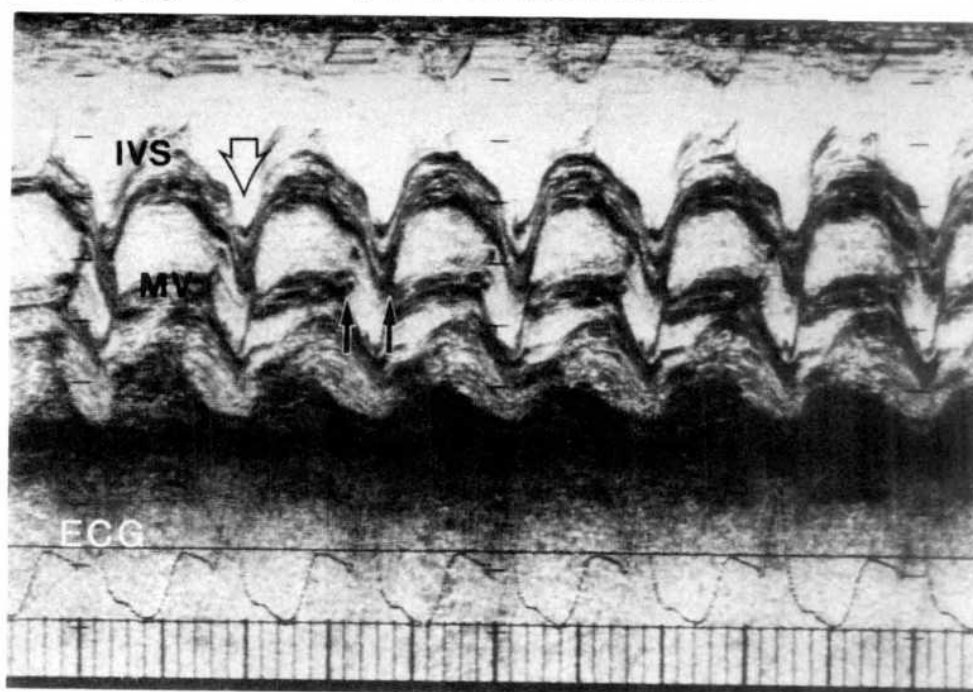


Fig. 3 Parasternal view of the mitral valve (MV) showing the regular mitral opening (arrows) seen with 1:1 conduction. The diagnosis at electrophysiological study was supraventricular tachycardia. Note the dilated right ventricle and reversed movement (open arrow) of the interventricular septum (IVS) caused by a coexisting ostium primum atrial septal defect.

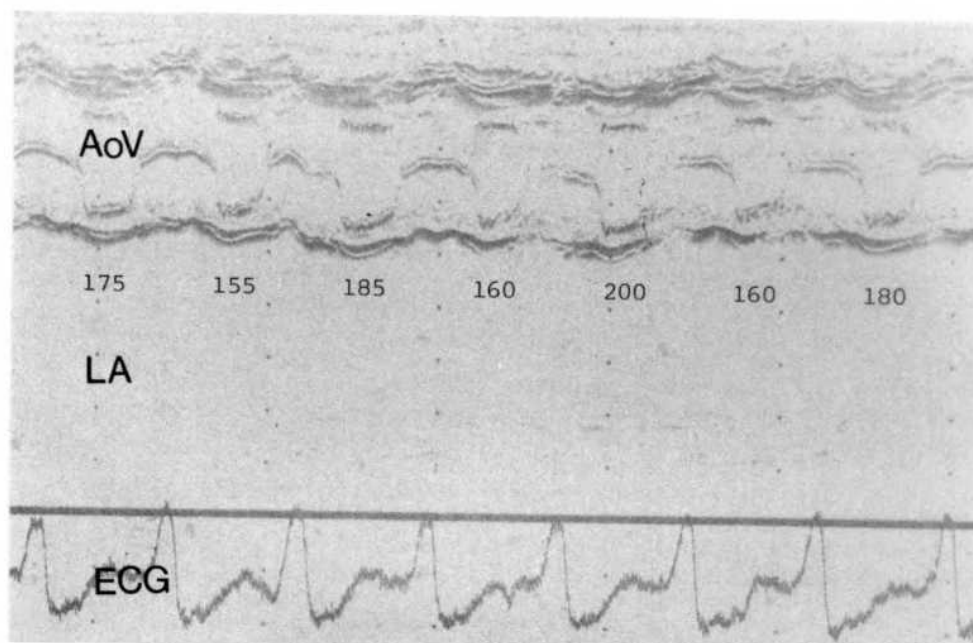


Fig. 4 Parasternal view of the aortic valve (AoV) and left atrium (LA) in ventricular tachycardia. The duration of aortic valve opening varies from beat to beat. Aortic valve opening times are given in ms.

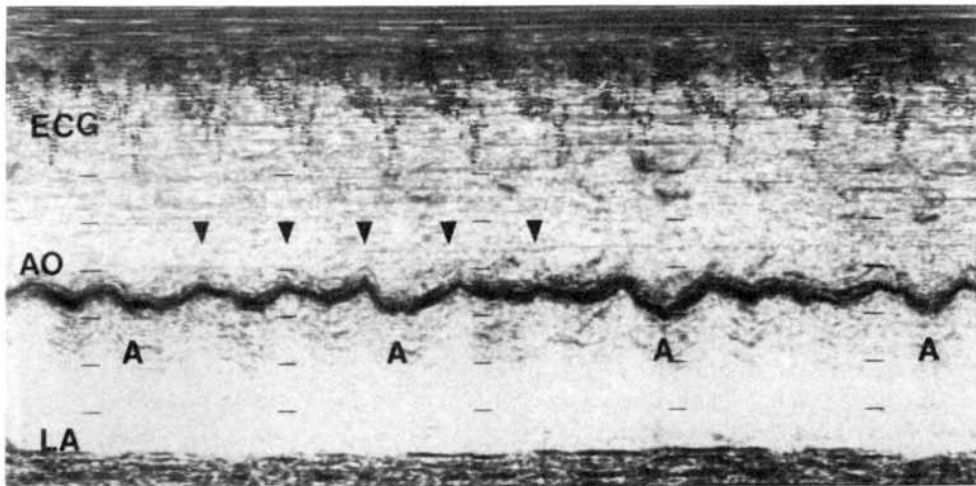


Fig. 5 Parasternal view through aorta (AO) and left atrium (LA) showing evidence of clearly dissociated atrial activity (A) on the posterior wall of the aorta. The arrows show aortic movement related to ventricular contraction. The electrocardiogram (ECG) is of poor quality. Note the absence of contraction of the posterior wall.

supraventricular tachycardia with 1:1 conduction (Fig. 7) and the fourth had atrial flutter with 2:1 conduction.

Discussion

Echocardiographic differentiation between supraventricular and ventricular tachycardia depends on iden-

tifying the relation between atrial and ventricular contraction. Patients with broad complex tachycardia and retrograde block of any degree almost certainly have ventricular tachycardia. The retrograde block can be demonstrated directly by showing dissociated atrial activity on the left or right atrial walls (Figs. 5 and 6) or indirectly by showing irregular mitral valve opening (Fig. 2). The echocardiographic appearance of the

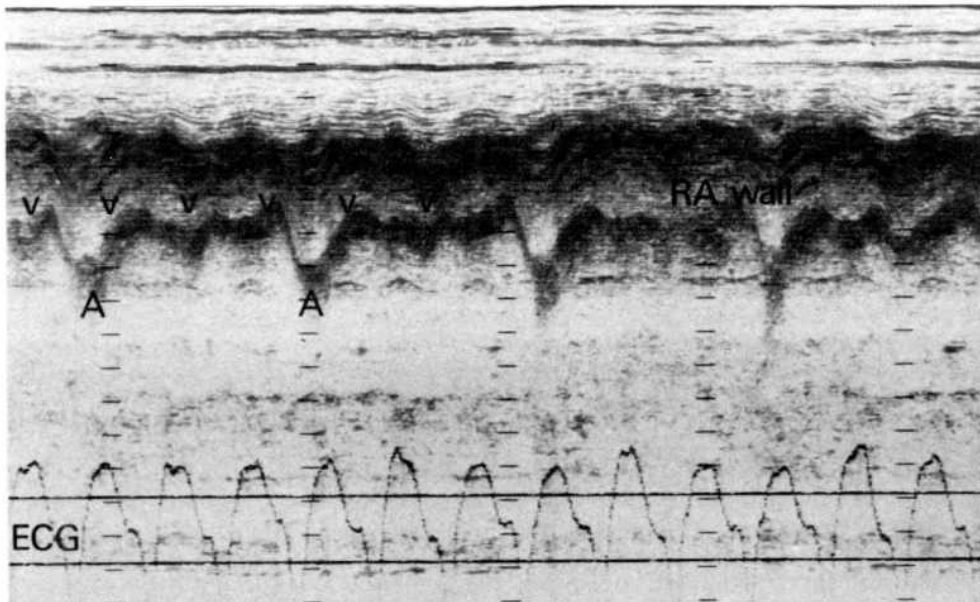


Fig. 6 Subcostal view of the right atrial wall (RA wall). The transmitted movement related to ventricular contraction (V) coincides with the electrocardiogram (ECG). Dissociated atrial contraction (A) is shown as clear posterior movement. Reproduced with permission of American Heart Journal.⁸

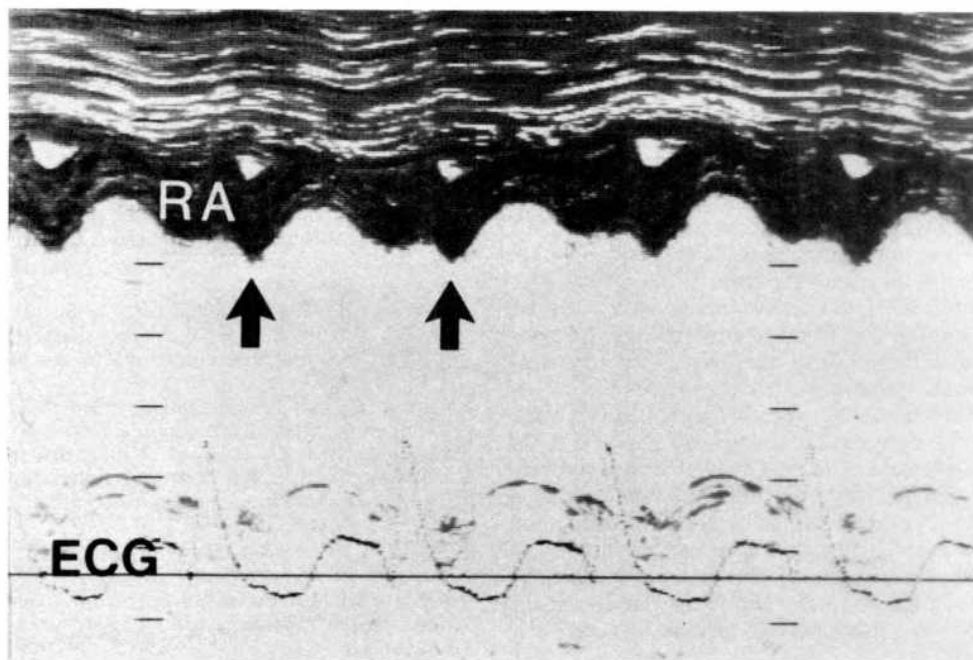


Fig. 7 Subcostal view of right atrial wall (RA) in supraventricular tachycardia in the same patient as in Fig. 3. There is a 1:1 relation between atrial contraction (arrows) and the QRS on the electrocardiogram (ECG).

mitral valve in broad QRS complex tachycardias was described by Manyari *et al.*⁴ They found a clear distinction in the variability of mitral valve opening between anterograde or retrograde conduction and atrioventricular dissociation. Their values of less than 22% variability of mitral opening and less than 12% variability of aortic opening with 1:1 conduction, and 68–129% mitral variability and 41–175% aortic variability in ventricular tachycardia with retrograde block accord with our results. They had only eight patients, however, with pacing simulated arrhythmias in three patients, and a maximum heart rate of 143 beats/min. Our study shows that variability of the time of mitral opening can clearly identify the relation between atrial and ventricular contraction in unselected patients with spontaneous arrhythmias with heart rates up to 225 beats per minute.

When anterograde block is present the diagnosis must be supraventricular tachycardia. In the event of 1:1 conduction the echocardiogram cannot at present be used to distinguish between supraventricular tachycardia and ventricular tachycardia. It may eventually be possible to tell whether conduction is anterograde or retrograde by timing atrial and ventricular contraction on the echocardiogram but present experience does not allow this.

Fortunately, 1:1 retrograde conduction is uncommon

in spontaneous sustained ventricular tachycardia with fast heart rates,⁹ and so echocardiographic confirmation of 1:1 conduction means that supraventricular tachycardia is the likely diagnosis. Obviously, the echocardiogram will not be used in isolation and electrocardiographic features will be taken into account as well.

The patients in this study may well be an atypical group as several were referred when they did not respond to initial treatment. In most cases they had been treated for supraventricular tachycardia, whereas we proved the presence of ventricular tachycardia in all the referred patients. Retrograde conduction may have been modified by the drugs they had received, and this may explain why no ventricular tachycardia with 1:1 retrograde conduction was seen.

Views of the mitral valve were of great value in all our patients, whereas aortic valve and left atrial views were less often helpful. Many of our patients had ischaemic heart disease with impaired left ventricular function and left atrial enlargement. This may explain why we did not see "A" waves on the posterior wall of the left atrium (Fig. 5) but did see them in the right atrium (Fig. 6). Other workers have found left atrial echocardiograms useful in the diagnosis of broad QRS complex tachycardias.⁷

M mode recordings of the left ventricle were gener-

ally of poor quality and were unhelpful. This was not surprising as most patients had left ventricular disease and ventricular contraction during ventricular tachycardia is incoordinate and is much reduced. "A" waves were not seen on the left ventricular traces in any patient.

The echocardiographic characteristics of various arrhythmias seen by subcostal scanning were described by Drinković, who was able to record the movement of the right atrial wall subcostally in all of 260 patients undergoing routine echocardiographic examination.^{6,10} Others have found that adequate subcostal images can be recorded in most patients examined in the coronary care unit.¹¹ One advantage of subcostal scanning is that it provides direct evidence of the timing of atrial contraction, and in these patients the right atrium and ventricle are less likely to be diseased or dilated than the left atrium and ventricle. Drinković reported the appearances of ventricular tachycardia with 1:1 retrograde conduction, pacing simulated ventricular tachycardia, and runs of ventricular extrasystoles.¹⁰ We have shown that the echocardiogram is equally helpful in confirming the diagnosis in spontaneous sustained ventricular tachycardia.

Although all the M mode recordings in this series were derived from the sector scan, it is possible to obtain satisfactory results with an M mode machine alone.^{4,6,10} This brings the technique within the capability of many more hospitals. We feel that echocardiography is of great value when the electrocardiogram alone cannot distinguish between supraventricular and ventricular tachycardia. With increasing experience of the technique and its interpretation the echocardiogram could become a standard investigation in the diagnosis of broad complex tachycardias.

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Interrelation between donor and recipient heart rates during exercise after heterotopic cardiac transplantation

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SUMMARY The interrelation between the rates of the innervated recipient heart and the denervated donor heart at rest, on standing, and during the different phases of maximal exercise was studied in nine patients 1-6 months after heterotopic cardiac transplantation. The resting heart rate was significantly higher in the donor heart compared with the recipient heart. Eight of the nine recipient hearts and none of the donor hearts showed an increase in heart rate on standing up. All patients were exercised using a Bruce protocol until fatigued. The increase in heart rate during the first three minutes of exercise was lower in the donor hearts (10.7(6) beats/min) than in the recipient hearts (30(4.8) beats/min) but the peak heart rates were almost identical (donor hearts 152.7(2.9) and recipient hearts 152(2.8) beats/min). Five of the nine donor hearts and none of the recipient hearts showed a significant increase in heart rate after cessation of exercise. Three minutes after exercise heart rate had decreased by only 0.2(5.7) beats/min in the donor hearts compared with 33.6(6) beats/min in the recipient hearts. In spite of these differences in response between the donor hearts and recipient hearts, there were significant correlations between the two heart rates in the same patient at rest, after the first three minutes of exercise, at peak exercise, and during recovery.

Heterotopic cardiac transplantation presents a unique opportunity to compare the responses of the innervated recipient heart and the denervated donor heart simultaneously to identical stimuli. Although there have been previous reports of changes in heart rate in the denervated donor heart to exercise in experimental¹ and clinical² orthotopic cardiac transplantation, there are no reports of similar studies after heterotopic cardiac transplantation.

The purpose of this study was to examine changes in heart rates of the donor and recipient hearts and their interactions during changes in posture and dynamic exercise. Such studies could be of value in clarifying the role of the nervous system in regulating heart rate during different phases of exercise and in understanding the cardiovascular dynamics of patients after heterotopic transplantation.

Patients and methods

Nine patients who had undergone heterotopic cardiac transplantation 1-6 months earlier were studied. The Table outlines the clinical characteristics of these patients, details of the underlying cardiac pathology of the recipient heart, data regarding the donor heart and drug treatment, and the results of the most recent cardiac biopsy (of the donor heart).

None of these patients was receiving beta blockers, digitalis, or other cardiac drugs, nor did they have diabetes or other diseases that could affect the autonomic nervous system. One patient was studied one month after operation, two three months, and the rest six months. In all patients both the donor and recipient hearts were in sinus rhythm.

OPERATIVE TECHNIQUE

Heterotopic cardiac transplantation involves the insertion of the donor heart into the right chest in parallel with the recipient heart. Anastomoses are carried out between the donor and recipient superior vena cavae, left atria, aorta, and pulmonary arteries.

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Accepted for publication 22 March 1985

Table Details of patients

Case No	Sex/age of recipient (yr)	Age of donor (yr)	Interval from operation to exercise (month)	Underlying pathology	Drugs	Recent biopsy findings
1	M/27	16	2	CCM	Imuran, cyclosporin A	No rejection
2	M/42	14	5	IHD	Prednisolone, imuran, cyclosporin A	No rejection
3	M/46	16	4	IHD	Prednisolone, imuran, cyclosporin A	Mild rejection
4	M/50	30	6	IHD	Prednisolone, imuran, cyclosporin A	No rejection
5	M/42	19	5	CCM	Prednisolone, imuran, cyclosporin A	Mild rejection
6	M/45	32	2.5	IHD	Imuran, prednisolone	Mild rejection
7	M/59	36	3	IHD	Imuran, prednisolone	No rejection
8	F/30	13	6	CCM	Prednisolone, imuran, cyclosporin A	No rejection
9	M/42	20	1	IHD	Imuran, cyclosporin A, diuretics	No rejection

CCM, congestive cardiomyopathy, IHD, ischaemic heart disease

This modified technique, where the vena cavae are anastomosed instead of the right atria,³ preserves the arteries to both sinoatrial nodes and the nerves to the recipient heart. In addition, aneurysmectomy with coronary artery bypass grafts to the recipient hearts were performed in six patients who had ischaemic heart disease (Table).

STUDY PROTOCOL

A modified 12 lead electrocardiogram was obtained at 25 mm/s before the start of exercise with lead V6R recorded instead of V2. The QRS complex from the donor heart produced the dominant positive vector in V6R whereas that from the recipient heart produced a dominant positive vector in V5 (Fig. 1). In addition, the configuration of the QRS complexes was compared with the preoperative electrocardiogram to help distinguish the complexes from the donor and recipient hearts in the different leads.

Baseline recordings were obtained after at least 10 minutes in the sitting position and after 30 seconds of standing. Exercise was then started on a computerised treadmill (Marquette Case) using the Bruce protocol.⁴ A three lead electrocardiogram was printed out in the first five seconds of each minute of exercise and at every minute of recovery for at least 12 minutes. The leads monitored were those that enabled clear separation of the donor and recipient QRS complexes and usually included V1, V6R, and another lead. Figure 1 shows recordings in a patient at rest and at peak exercise. Heart rate was calculated from the mean of at least three consecutive RR intervals for each heart at rest, at every minute of exercise, at peak exercise, and at every minute of recovery for at least 12 minutes.

CONTROL SUBJECTS

Eight healthy age matched male volunteers served as control subjects and followed the above protocol.

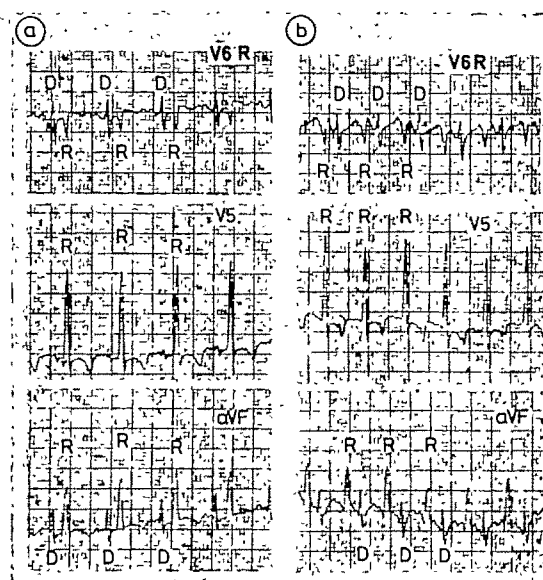


Fig. 1 Electrocardiograms from a patient (a) at rest and (b) at peak exercise showing separate identification of donor and recipient QRS complexes.

Their heart rates were recorded at rest, on standing, and at every minute of exercise; and during recovery for 12 minutes.

STATISTICAL TECHNIQUES

Standard paired *t* tests, χ^2 tests, and correlations were used to compare changes between the two heart rates. Results are expressed as mean (one standard error of mean).

Results

RESTING HEART RATES

The resting heart rate was significantly higher in the donor hearts (106(2) beats/min) than in their respective recipient hearts (95(6) beats/min; $p < 0.05$) (Figs. 2a and 3a). The donor heart rate was lower than the recipient heart rate in only one patient. There was a significant positive correlation between the two resting heart rates (Fig. 3) ($r = 0.84$; $p < 0.01$). The resting heart rates of both the donor and recipient hearts were independent of age, sex, underlying cardiac pathology, duration since operation, drug treatment, and biopsy results.

CHANGES IN HEART RATE

With posture

Eight of the nine recipient hearts showed an increase in heart rate (by 7(2) beats/min) on standing up compared with 0 of nine donor hearts ($p < 0.01$).

During exercise

Exercise was stopped in all patients because of fatigue at 7.4(0.9) minutes (range 3–10 minutes). The increase in heart rate during the first three minutes of exercise was lower in the donor heart (10.7(3.6) beats/min) than in the recipient heart (30(4.8) beats/min; $p < 0.001$) (Fig. 2b). The magnitude of increase in the two heart rates showed, however, a significant correlation during this period ($r = 0.75$; $p < 0.05$) (Fig. 3b). During the later stages of exercise, heart rate increases in the donor heart were either similar to, or greater than, those in the recipient heart so that at peak exercise the two heart rates were not significantly different in the group as a whole (147(3.3) beats/min in donor hearts compared with 152(2.8) beats/min in recipient hearts) (Fig. 2a). In addition, the two heart rates at peak exercise showed a significant correlation ($r = 0.81$; $p < 0.01$) (Fig. 3c).

After cessation of exercise

Five of the nine donor hearts but none of the recipient hearts showed an increase in heart rate after cessation of exercise ($p < 0.05$). The donor heart rate increased by 10.8(2) beats/min in these five patients, and a further two patients maintained peak heart rates for at least three minutes after exercise was stopped. The heart rate was equal to, or greater than, that at peak exercise for 3.2(0.7) minutes in the nine donor hearts during recovery. This immediate postexercise tachycardia was most prominent in magnitude and duration in the three patients exercised within three months of operation (+7, +13, and +16 beats/min; 4 minutes, 5 minutes, and 6 minutes respectively). The number of patients studied is, however, too small for statistical comparison. At three minutes after exer-

cise, heart rate had decreased by only 0.2(5.7) beats/min in the donor hearts compared with 33.6(6) beats/min in the recipient hearts ($p < 0.001$) (Fig. 2c). Despite this there was a good correlation in the changes in heart rate between the two hearts ($r = 0.83$; $p < 0.01$), as patients showing an increase in donor heart rate after exercise showed the smallest decrease in recipient heart rate measured over the same period (Fig. 3d).

The subsequent rate of decrease in the two heart rates was similar ($-12.8(1.5)$ beats/min in donor hearts compared with $-12(2.7)$ beats/min in the recipient hearts at 3–6 minutes after exercise) (Fig. 2c).

There was a weak trend when the magnitude of the heart rate decrease in the two hearts during this period was compared ($r = 0.62$; $p < 0.05$).

Figure 4 illustrates the changes in rate in the donor and recipient hearts in a typical patient studied at four weeks and shows the increase in donor heart rate after cessation of exercise.

RELATION OF RESTING RATE AND RECOVERY RATE

The resting heart rate did not correlate with the changes in the first three minutes of exercise or recovery in the donor hearts but showed significant inverse correlations in the innervated recipient hearts ($r = 0.85$; $p < 0.01$ and $r = 0.81$; $p < 0.01$ respectively). The increase in heart rate during the first three minutes of exercise correlated inversely with the decrease in heart rate during the first three minutes of recovery in both the donor ($r = 0.79$; $p < 0.01$) and recipient hearts ($r = 0.76$; $p < 0.01$) separately and overall ($r = 0.87$; $p < 0.001$).

COMPARISONS BETWEEN RECIPIENT HEARTS AND CONTROL SUBJECTS

The resting heart rate in the heterotopic recipient hearts (95(6) beats/min) was significantly greater than in the controls (76(2) beats/min) ($p < 0.001$). Nevertheless, the increases in heart rate on standing (7(2) beats/min in the heterotopic recipient heart and 10(4) beats/min in the control subjects) and during the first three minutes of exercise (30(4) and 29(3) beats/min respectively) were similar. The control subjects exercised longer, however, and reached higher heart rates (14(1) minute and 183(9) beats/min respectively) than the transplant patients (8(2) min and 152(2.8) beats/min; $p < 0.01$ and $p < 0.001$ respectively). The decrease in heart rate in the first three minutes after the cessation of exercise was similar (expressed as a percentage of the total heart rate increase) in both the controls and recipient hearts ($-62(3)\%$ and $-57(8)\%$).

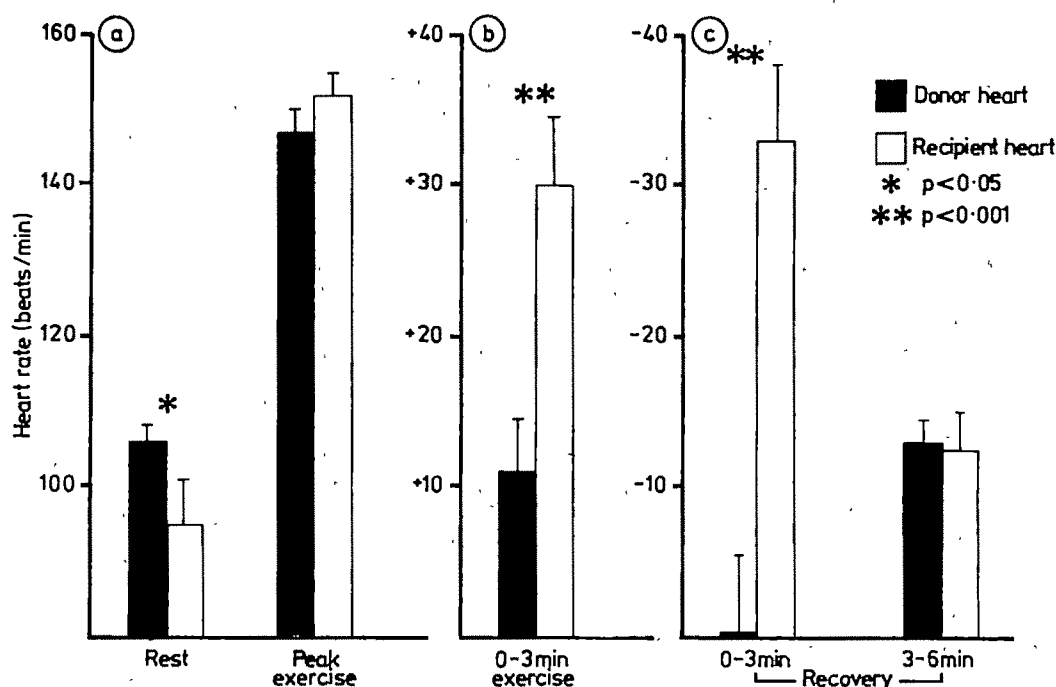


Fig. 2 Heart rates (a) at rest and at peak exercise, (b) in the first three minutes of exercise (% increase), and (c) at recovery (% decrease) in the donor and recipient hearts.

Discussion

The interrelation of the changes in the rate of the denervated and innervated hearts, in the same subject during identical stimuli, is a useful model to study the contribution of the nervous system to heart rate control since current evidence suggests that the donor heart remains denervated after transplantation,⁵ and the nerves to the recipient heart are not severed during heterotopic transplantation. Although this is the main factor that can explain the differences in response between the two hearts, other possible factors include the possible inhibitory influence of baroreceptor mediated stimuli (although these are of less importance during exercise⁶) on the recipient heart due to the added random ejection by the donor heart. In addition, the position of the heterotopic donor heart, in the right side of the chest, and the peculiar mode of atrial filling and aortic emptying produced by the specific type of anastomosis may influence its response. Although the recipient heart may have intact nerves and a patent arterial supply, the response to exercise can be modified by the underlying cardiac pathology (congestive cardiomyopathy or ischaemic heart disease). Comparison of the responses of the recipient heart with those of healthy

controls suggests, however, similarity in the changes in heart rate response to standing during the first three minutes of exercise and recovery, although the resting heart rate, duration of exercise, and peak heart rate were significantly different. This suggests that it would be valid to compare the heart rate changes in the donor heart with those in the recipient heart of the same patient.

The resting heart rate of the donor heart was higher than that of the corresponding recipient heart in eight of nine patients, and this finding is consistent with vagal and sympathetic denervation.⁷ The heart rate of the heterotopic donor hearts that we observed is comparable to those found after pharmacological autonomic blockade,⁷ and is similar to the heart rate in patients with orthotopic human transplants in our own experience and that reported from other centres.^{2,8} The resting heart rate in the innervated recipient heart was inversely related to heart rate changes in the early minutes of exercise and recovery. This indicates that, with higher vagal tone, resting heart rate is lower and rises rapidly during early exercise owing to vagal withdrawal and falls rapidly after exercise owing to vagal stimulation. The resting heart rate in the recipient hearts was, however, significantly higher than in the controls and is probably related to

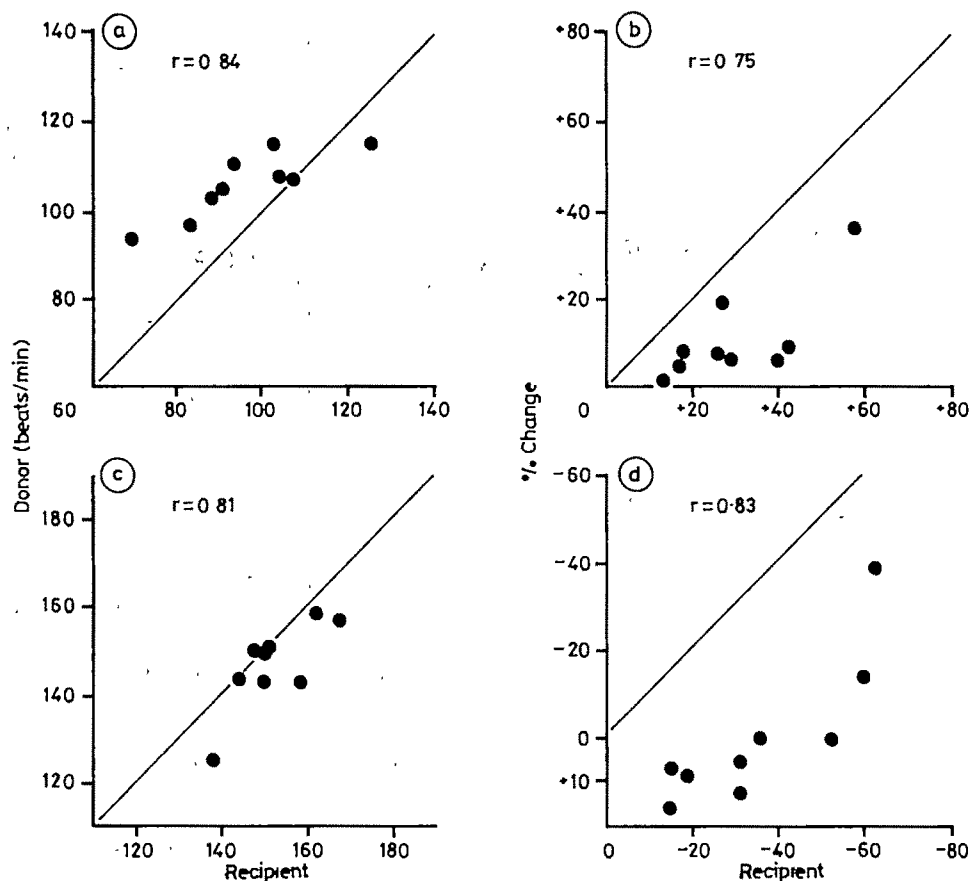


Fig. 3 Correlation between the increase in donor and recipient heart rate (a) at rest, (b) at 0-3 min exercise, (c) at peak exercise, and (d) at 0-3 min of recovery.

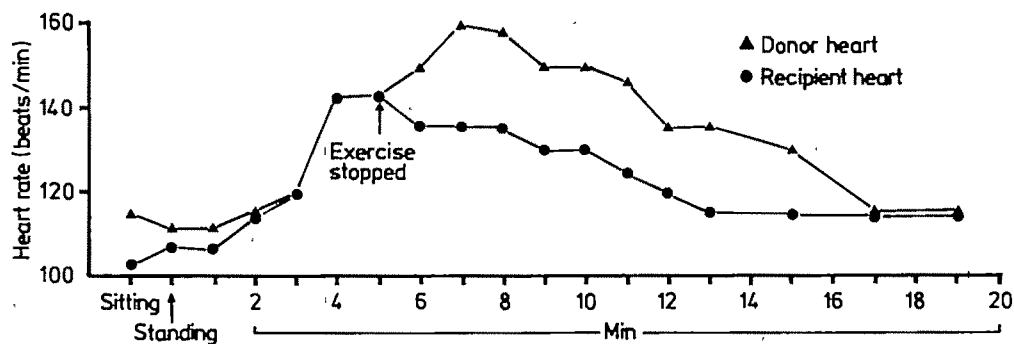


Fig. 4 Changes in heart rate in a patient at rest, on standing, and during and after exercise in the donor and recipient hearts. Note the similar heart rate at peak exercise and increase in heart rate after exercise in the donor heart

the fact that these are severely diseased hearts. A lack of immediate increase in heart rate on standing up in the donor hearts is consistent with denervation,⁹ and contrasts with the increase seen in the innervated recipient hearts.

Previous experimental work has shown that the autotransplanted canine heart is capable of normal work capacity.^{2,10} There are, however, pronounced differences in the initial response to exercise between the denervated and normal canine heart. An increase in heart rate predominates in the normally innervated heart,¹¹ whereas increases in stroke volume predominate in the denervated heart¹² with little initial heart rate increase.^{2,13} We have seen only a small increase in heart rate in the initial three minutes of exercise in the denervated donor heart whereas the corresponding increase in the innervated recipient heart was threefold. This slow initial acceleration of the donor heart¹⁴ is consistent with the reports of Pope *et al* in human orthotopic transplants.² In addition, we have observed that the magnitude of initial heart rate increase in the innervated and denervated hearts correlated, suggesting that even at this low level of exercise there may be some chronotropic mechanisms that are common to the two hearts. These may be due either to low concentrations of circulating catecholamines or to some undefined intrinsic regulation in response to increased venous return.

During the latter phases of exercise the heart rate increase in the donor and recipient hearts was variable, but in general the two heart rates tended to converge so that at peak exercise the two heart rates were similar. This is of particular interest and suggests that at peak exercise non-neural mechanisms—for example, plasma catecholamines, which are at their maximum at peak exercise^{14,15}—may be the chief mechanism and that any upregulation in β receptor density¹⁶ and affinity in the denervated heart may almost exactly compensate for the absence of sympathetic nerve stimulation.

The greatest dissociation in the heart rate response of the denervated donor heart and innervated recipient heart was observed after the cessation of exercise. While the innervated heart rate decreased rapidly, the denervated hearts showed little change overall. Indeed, the heart rates were increased above those observed at peak exercise in five donor hearts for several minutes. These changes have not been reported before, either in experimental denervated hearts or after orthotopic transplantation. This may be due to the fact that in previous reports of exercise in orthotopic transplantation the studies were performed at 12–61 months² or at 7–18 months.⁸ By contrast, our patients were exercised much earlier (1–6 months). The postexercise tachycardia was most pronounced in the three patients exercised under three months and may be a feature of the early months after cardiac transplantation. The mechanism(s) of these changes is unknown but may be due to the heightened

response of the donor heart to the circulating catecholamines, which have been shown to continue to increase after exercise has stopped.¹⁷ In spite of the pronounced difference in heart rate changes between the two hearts during the first three minutes of recovery, there is a close correlation in individual patients suggesting the presence of non-neural linked mechanisms affecting both hearts.

This study has served to identify the specific interrelations between the heart rate at rest and the response during different phases of dynamic exercise. We hope that this will be of value in understanding the physiological mechanisms governing heart rate changes and help in the management of patients after cardiac transplantation or those with automatic nervous disorders.

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Prevalence and clinical significance of aortic valve prolapse

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SUMMARY The prevalence and clinical significance of aortic valve prolapse were determined prospectively in 2000 consecutive patients undergoing routine clinical cross sectional echocardiography. Two hundred and twelve patients were excluded because the aortic cusps were not adequately visualised. Aortic valve prolapse was defined as downward displacement of cuspal material below a line joining the points of attachment of the aortic valve leaflets. Twenty four cases of aortic valve prolapse (1.2%) were identified. The patients were aged 12-64 years and nine were women. All had underlying valvar heart disease and the commonest lesion (in 11 cases) was prolapse of the larger cusp in bicuspid valves. Aortic valve prolapse was seen in four patients with mitral valve prolapse (two with severe regurgitation), one of whom had marfanoid aortic root dilatation. The remaining examples of aortic prolapse were seen in patients with various disorders including one with pulmonary atresia, two with aortic root disease (one with dissection and one with idiopathic dilatation), and one case of severe mitral regurgitation. Valves destroyed by infective endocarditis were seen in two cases. Aortic valve prolapse may be detected in various cardiac disorders and does not imply the presence of aortic regurgitation, but when bicuspid aortic valves are present it may well be important in producing such regurgitation. Although aortic valve prolapse may be associated with severe forms of mitral valve prolapse, these patients rarely have aortic regurgitation.

In patients with aortic regurgitation and a normal or dilated aortic root the M mode or cross sectional echocardiographic appearances of the aortic valve may be surprisingly normal. Often the only apparent abnormality is thickening of the valve or restricted cusp motion.¹ Aortic regurgitation in a dilated aorta is thought to be the result of malalignment and inadequacy of the cusps, but the valve may be competent and appear to be normal despite a grossly dilated aortic root.² The mechanism of aortic regurgitation in the absence of root dilatation is also often unclear, especially in bicuspid aortic valves, but anatomical studies suggest that such valves are usually regurgitant.³ Aortic valve prolapse has been reported in surgical and necropsy studies^{2,4} and may also be shown by echocardiography in patients with mitral valve prolapse.^{5,6} The thin aortic valve cusps are less echo reflective than those of the more voluminous mitral valve, and therefore it may be more difficult to iden-

tify aortic valve prolapse. With the progressive improvement in image resolution by cross sectional echocardiography such features may be more readily seen.

The purpose of this study was to determine the prevalence of aortic valve prolapse in patients undergoing routine cross sectional echocardiography and to determine the relation of aortic valve prolapse to mitral valve prolapse and aortic regurgitation.

Patients and methods

Two thousand consecutive patients aged 9 to 83 years with all forms of heart disease who underwent routine M mode and cross sectional echocardiography were included. Patients with prosthetic aortic valves were excluded. The presence of an aortic early diastolic murmur was noted and graded out of four. The clinical details of patients were extracted from the case notes.

ECHOCARDIOGRAPHIC TECHNIQUE

Cross sectional echocardiograms were performed on

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Accepted for publication 7 May 1985

Hewlett-Packard phased array apparatus (model 77020A) with a 3.5 or 5 MHz transducer. Complete echocardiographic studies in the parasternal, sub-xiphoid, suprasternal, and apical views were routinely obtained and recorded on half inch (13 mm) video cassette tapes. To minimise difficulties with transducer angle and positioning we analysed only images obtained with the patient in the semi-left lateral position and taken in the long axis parasternal view. We measured left ventricular cavity size in systole and diastole (minimum and maximum cavity size respectively) and aortic root dimensions at end systole.

DEFINITIONS

Aortic valve prolapse was diagnosed when either or both of the right or non-coronary aortic valve cusps (seen in the cross sectional echocardiographic long axis view) showed backward bowing towards the left ventricle beyond a line joining the points of attachment of the aortic valve leaflets to the annulus (Fig. 1).

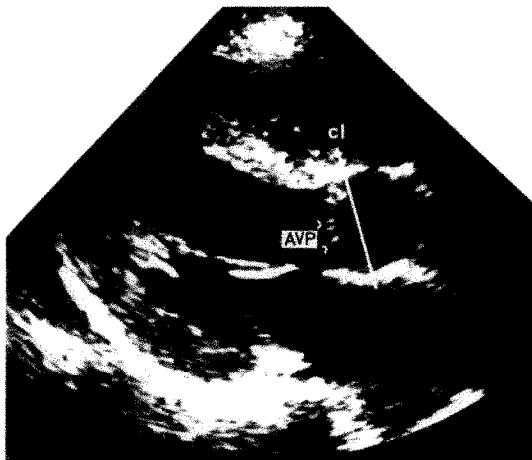


Fig. 1 Long axis parasternal cross sectional echocardiogram in a patient with a bicuspid aortic valve and mild to moderate aortic stenosis. Aortic valve prolapse (AVP) is clearly seen with cuspal material below a line (cl) joining the points of attachment of the aortic leaflets to the annulus.

Mitral valve prolapse was diagnosed when there was a systolic mitral click and a late systolic murmur or both. Systolic buckling or hammocking of the mitral valve detected by M mode echocardiography or mitral valve prolapse detected by cross sectional echocardiography also had to be present.

Aortic root dilatation was diagnosed when the end systolic aortic measurement exceeded 3.8 cm (2 SD from normal).

A *bicuspid aortic valve* was identified if either of the following was present (a) if in a diastolic short axis parasternal view the aortic valve did not form a normal Y pattern with commissures at 2, 6, and 10

o'clock and only two well defined cusps were identified with a single closure line; (b) if inspection at operation or necropsy showed a bicuspid aortic valve.

Results

Of the 2000 patients, 216 had no evidence of cardiac disease and in 212 the aortic valve cusps were not adequately imaged. The presence of valvar calcification made the aortic valve much more difficult to image and the aortic valve was seen sufficiently well in only 38 of 86 such patients. A total of 325 patients had rheumatic heart disease, 296 had valve replacement, 336 had coronary heart disease, and 320 had aortic valve disease (of whom 37 clearly displayed bicuspid aortic valve). Hypertrophic cardiomyopathy was seen in 63, congestive cardiomyopathy in 126, and mitral valve prolapse in 68 cases. The remaining 260 patients had various congenital heart diseases, pericardial disease, hypertension, and other less common conditions.

In patients without cardiac disease, the point of aortic valve closure was always above a line joining the valve attachments. We identified 24 patients with aortic valve prolapse, all of whom had evidence of cardiac disease; the Table shows their clinical details. They were aged 12 to 64 years and nine were women. In 10 the right cusp, in six the non-coronary cusps, and in eight both cusps had prolapsed. In seven cases the thickness of the aortic valve appeared to be normal, in one patient with infective endocarditis there appeared to be a vegetation on the aortic valve, and the remainder had some valve thickening. In only one case was there evidence of aortic valve flutter (valve destroyed and flail after endocarditis). Eleven of the 37 patients with obviously bicuspid valves had aortic valve prolapse, two had associated subvalvar aortic stenosis, and two had previously undergone aortic valvotomy. In seven, prolapse of the larger cusp was seen (Figs. 2a, 2b, and 3) and in four there was prolapse of both cusps (Figs. 1 and 4).

Only four of the 68 patients with mitral valve prolapse had aortic valve prolapse and seven had aortic root dilatation; one patient had both. Aortic valve prolapse was identified in only three patients without root dilatation (Fig. 4). Two other patients had aortic valve prolapse together with a dilated aortic root due to unknown causes or pulmonary atresia. Aortic valve prolapse in three patients was associated with rheumatic mitral and aortic valve disease. Although all these patients had aortic regurgitation, the predominant haemodynamic abnormality was related to the mitral blood flow. Seven patients with aortic valve prolapse did not have clinical evidence of aortic regurgitation. They included one patient with a bicuspid aortic

Table Clinical details of patients with aortic valve prolapse

Case No	Age (sex)	EDM/4	Blood pressure (mm Hg)	Prolapse of MVP BICAV	Aortic root size	Comment
1	67(M)	—	140/90		N	Rh, MVD, AVG 20 mm Hg, CAD
2	15(M)	2	110/70	+	N	AVG 35 mm Hg, SVAS
3	48(M)	2	150/70	*	N	Flail AV cusp, SBE
4	22(F)	2	110/50		E	Pulmonary atresia
5	68(M)	4	150/30		E	Marfan's syndrome
6	57(M)	3	140/45		E	ARD
7	59(F)	2	125/65		N	Rh MVD, AVG 25 mm Hg
8	34(F)	3	160/55		E†	
9	69(F)	—	130/80		N	Severe MR
10	13(M)	1	100/80	+	N	AVG 55 mm Hg, MVR, AVOT
11	16(F)	—	110/70	+	N	
12	28(F)	1	110/60	+	N	SVAS, AVOT
13	22(F)	2	120/65	+	N	AVG 40 mm Hg
14	24(M)	2	150/70	+	N	AVG 30 mm Hg
15	16(M)	1	120/85	+	N	AVG 25 mm Hg
16	58(F)	—	125/80		N	Rh MVD, trivial AVS
17	27(M)	3	150/60		E	AR due to SBE
18	54(F)	—	140/70		N	Severe MR
19	63(M)	—	130/80	†	N	Severe MR
20	25(M)	1	130/70	+	N	
21	26(M)	—	110/70		N	Mild MR
22	60(M)	—	130/80	+	N	Mild AVS, CAD
23	19(M)	4	150/40	+	N	AVG 30 mm Hg
24	27(M)	3	130/70	+	N	

AV, aortic valve; AVG, aortic valve gradient (mm Hg); AVOT, valvotomy; AVS, aortic valve stenosis; AR, aortic regurgitation; ARD, idiopathic aortic root dilatation; Rh, rheumatic; BICAV, bicuspid aortic valve; MVD, mitral valve disease; MR, mitral regurgitation; MVP, mitral valve prolapse; MVR, mitral valve replacement; CAD, coronary artery disease; SVAS, subvalvar aortic stenosis; SBE, subacute bacterial endocarditis

EDM/4, early diastolic murmur graded out of 4

*AV destroyed by infection †Aortic dissection present. ‡Redundant regurgitant mitral valve with no obvious prolapse.

+, present; —, absent; E, enlarged; N, normal

valve, one with mild rheumatic aortic valve disease, and all four patients with mitral prolapse.

Discussion

We examined the prevalence of aortic valve prolapse in 2000 consecutive patients undergoing routine echocardiography. Although only 1.2% of patients had aortic valve prolapse, 30% of those with a bicuspid aortic valve showed prolapse. Both mitral and aortic valve prolapse were found in four patients, one of whom had marfanoid aortic root dilatation; aortic valve prolapse without root dilatation was seen in only three patients, two of whom had severe mitral regurgitation. Aortic valve prolapse was also seen in three cases with rheumatic heart disease and two with infective endocarditis. This latter finding is contrary to that reported by Becher *et al* who often found aortic valve prolapse in cases of endocarditis.⁷ Aortic valve prolapse is known to be associated with a subaortic ventricular septal defect, but no such patient was identified in our series.²

There are several problems with the echocardiographic diagnosis of aortic valve prolapse. The aortic valve cusps may not be clearly seen and even with apparatus giving the highest resolution currently available, adequate images were obtained in only

89.3% of patients. There is no standard definition of aortic valve prolapse; that chosen for this study was of unknown sensitivity and specificity but in each case there was clear evidence of downward displacement and cuspal material below the aortic valve annulus. We excluded those echocardiograms that were not aligned along the left ventricular/aortic long axis since such echocardiograms often simulate aortic valve prolapse. This situation is analogous to that in mitral valve prolapse may be demonstrated in patients without evidence of cardiac disease.⁸

Aortic valve prolapse was most commonly found in bicuspid aortic valves and this confirms the findings of a recent study.⁹ We found that in all cases the echocardiographically larger cusp prolapsed, but in four cases both cusps appeared to prolapse. Bicuspid aortic valves dome upwards in systole and prolapse downward in diastole, reflecting their cuspal distortion and fusion. Ejection clicks are typical of a bicuspid aortic valve; however, some patients may have a prolonged and loud closure sound,¹⁰ possibly due to the sound of cuspal prolapse. Bicuspid aortic valves may be predominantly regurgitant,^{3,11} and in the absence of infection and extensive calcification aortic valve prolapse is presumably one of the mechanisms responsible for such regurgitation. There were 212 patients in whom the aortic valve cusps could not be

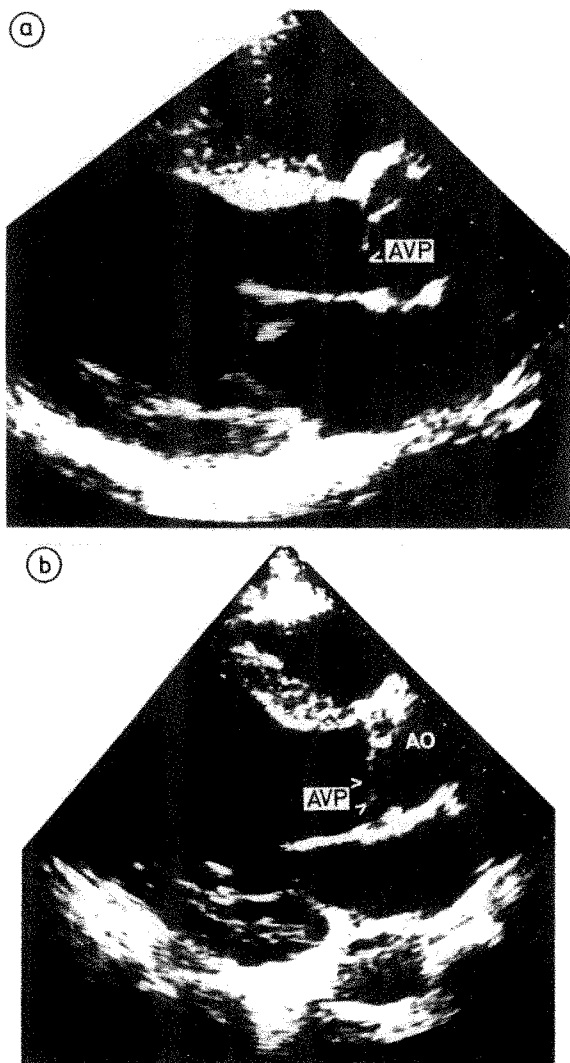


Fig. 2 Two echocardiograms of patients with prolapse of the larger cusp of a bicuspid aortic valve. (a) Prolapse in a patient with no aortic regurgitation. (b) Similar appearance of the valve in a patient with severe valvular regurgitation. AO, aorta; AVP, aortic valve prolapse.

adequately visualised and the cusps were obscured in 38 of the 86 with aortic valve calcification. A substantial proportion of the latter are likely to have had bicuspid aortic valves and therefore aortic valve prolapse may well be more common than indicated by this study.

An association between aortic valve prolapse and mitral valve prolapse has been reported by others. Sahn *et al* identified aortic root dilatation in 85% of

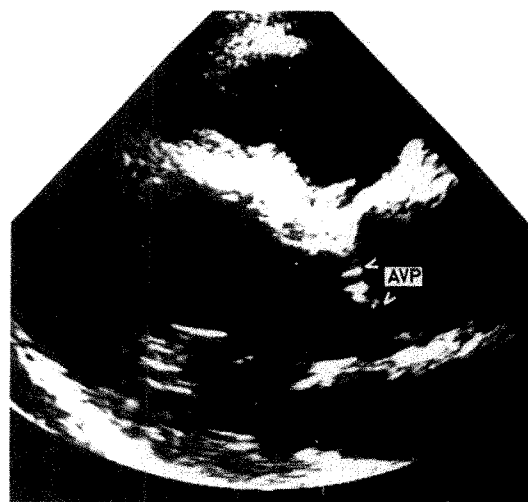


Fig. 3 Echocardiogram showing prolapse of both aortic valve cusps in a patient with mild aortic stenosis only and no regurgitation. AVP, aortic valve prolapse.



Fig. 4 Aortic valve prolapse in a patient with a normal sized aortic root and severe mitral regurgitation due to mitral valve prolapse. There was no clinical or angiographic evidence of aortic regurgitation. AVP, aortic valve prolapse.

patients with mitral valve prolapse¹² and aortic valve prolapse was seen in 20% of such patients.⁵ In patients with associated aortic and mitral valve prolapse, aortic regurgitation was seen in four of 17⁵ and eight of 12 cases.¹³ Our findings contrast with these reports, since only seven of our 68 cases of mitral valve prolapse had aortic root dilatation and four of the seven had skeletal or other manifestations of Mar-

fan's syndrome. Only three patients without aortic root dilatation showed aortic valve and mitral valve prolapse, and two of these had severe mitral regurgitation requiring valve replacement. No patient had clinical evidence of aortic regurgitation. Aortic root dilatation or severe mitral regurgitation are manifestations of a more extreme form of the developmental connective tissue abnormality (unlike cases with minor echocardiographic mitral valve prolapse⁸) and they may represent a group with multivalvar myxomatous degeneration or a formes frustes of Marfan's syndrome.^{5,14}

In conclusion, aortic valve prolapse was an infrequent finding in patients undergoing routine clinical echocardiography. Although these findings may represent an echocardiographic phenomenon rather than a diagnosis, in each case there was other evidence of valve disease, unlike the situation in individuals without evidence of valve disease in whom mild mitral valve prolapse may be demonstrated by echocardiography. In aortic root dilatation, the prolapse may occur with the formes frustes of Marfan's syndrome, presumably because of a defect in collagen metabolism, as occurred in the three patients with mitral valve prolapse without aortic root dilatation. In our series aortic valve prolapse was most commonly seen in the larger cusp of a bicuspid aortic valve. Three cases of rheumatic heart disease with predominant mitral valve involvement and two cases of infected valves were also seen. Presumably aortic valve prolapse may be the cause of aortic regurgitation, particularly in bicuspid aortic valves, valves destroyed by infection, and those malaligned because of root dilatation. Aortic valve prolapse did not imply the presence of aortic regurgitation, especially when aortic valve prolapse was associated with mitral valve prolapse.

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Embolisation procedures in congenital heart disease

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SUMMARY Eight therapeutic embolisation procedures were performed by the transcatheter technique in seven patients with congenital heart disease. After surgical correction of tetralogy of Fallot (four patients), catheter embolisation was used to occlude two large aortopulmonary collaterals (one patient), three small aortopulmonary collaterals (one patient), and two Blalock-Taussig shunts (two patients). In two patients congenital coronary anomalies were occluded—a coronary arteriovenous malformation and a coronary artery/bronchial artery anastomosis. In one patient a pulmonary arteriovenous malformation was embolised.

Detachable balloons were used to occlude six large arteries, the three small arteries were occluded with small gelfoam fragments, and the pulmonary arteriovenous malformation was occluded with multiple steel coils and large gelfoam pieces. Successful occlusion was achieved in all cases. No complications were encountered and the procedure was well tolerated even in the two patients receiving postoperative intensive care.

Therapeutic embolisation in suitable cases is a safe and effective alternative to surgery and the detachable balloon technique is effective in occluding high flow vessels.

The scope and feasibility of interventional radiological techniques have increased dramatically in recent years. Although therapeutic embolisation procedures are now widely used in various clinical settings, their application to congenital heart disease has been limited.

Surgery remains the generally accepted treatment for significant arteriovenous fistulous connections related to the heart and great vessels. Access to these structures and their identification may be difficult, particularly when repeated operations are necessary. Moreover, it may be impossible to decide which structures may be ligated safely, for example when there is a dual blood supply to the lungs from both the pulmonary and systemic arterial systems. We describe here the application of embolisation techniques to various types of congenital heart disease.

Patients and methods

Between 1981 and 1984 therapeutic embolisation procedures were performed in six patients aged 3-67 years at this hospital, and one patient aged 21 years at the Westminster Hospital (see Table).

Four patients with tetralogy of Fallot had undergone corrective surgery. They had all undergone surgical palliation earlier in life by insertion of Blalock-Taussig shunts, in one case bilaterally. After corrective surgery, two had important residual aortopulmonary collaterals and two had patent Blalock-Taussig shunts. One of these Blalock-Taussig shunts had been ligated at corrective surgery (case 2).

Two patients had primary coronary vascular malformations—one had a very large circumflex artery to coronary sinus fistula associated with aneurysmal dilatation of the coronary sinus (case 7); the other had a large circumflex to bronchial artery anastomosis as well as a severe localised and proximal stenosis of the left anterior descending coronary artery (case 1).

One patient who had a large pulmonary arteriovenous malformation was cyanosed and polycythaemic (haemoglobin, 17 g/dl) (case 3). He had presented with a cerebellar infarct.

In all cases the patient's clinician had formed the view that treatment was indicated and that surgery should be undertaken if attempts at therapeutic embolisation failed. Informed consent to the embolisation procedure was obtained from either the patient or his parents.

The method of therapeutic embolisation depended on the size of the vessel to be occluded and the type of anomaly. The following methods were used for

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Accepted for publication 13 May 1985

Table Embolisation procedures in patients with congenital heart disease

Case	Age(yr)/sex	Clinical	Previous surgery	Vascular abnormality	Embolisation method	Result of embolisation
1	67 M	Angina	None	Circumflex-bronchial arterial anastomosis. Stenosis of LAD coronary artery	8 mm silicone balloon (angioplasty at same procedure)	Successful. Repeat angiogram 7 months later confirmed occlusion
2	11 M	Tetralogy of Fallot	(1) Left B-T shunt (2) Complete correction. Ligation of B-T shunt	Patent left B-T shunt	Latex 12 mm balloon	Successful
3	52 M	Cerebellar infarct. Polycythaemia secondary to pulmonary arteriovenous malformation	None	Large single pulmonary arteriovenous malformation	(1) Steel coils (2) Steel coils and gelfoam	Successful. Initial procedure reduced the flow. The second produced total occlusion
4	21 F	Tetralogy of Fallot	(1) B-T shunt (2) Complete correction	Two large systemic collaterals from descending thoracic aorta	Two latex 12 mm balloons	Successful
5	4 F	Tetralogy of Fallot Complete AV septal defect, Down's syndrome	(1) Left B-T shunt (2) Right B-T shunt (3) Complete correction. Left B-T shunt ligated	Patent right B-T shunt	4 mm silicone balloon	Successful (died 3 weeks later)
6	3 F	Tetralogy of Fallot	(1) Right B-T shunt (2) Complete correction. Right B-T shunt ligated	Three enlarged systemic collaterals/bronchial arteries from descending aorta	Small gelfoam fragments	Successful
7	16 M	Symptom free, cardiomegaly. Reversible myocardial ischaemia due to coronary steal	None	Large circumflex coronary artery-coronary sinus fistula and aneurysm	Latex 12 mm balloon	Successful

B-T, Blalock-Taussig; AV, arteriovenous; LAD, left anterior descending.

embolisation: detachable balloons (five cases), silicone mini balloon (Becton-Dickinson) (cases 1 and 5), and latex balloons (Ingenor) (cases 2, 4, and 7); steel coils (William Cook Europe Aps) (case 3); and gelfoam (Sterispon, Allen and Hanburys) (cases 3 and 6).

Silicone mini balloons can be used to occlude vessels up to 8 mm in diameter. The smaller mini balloon (4 mm diameter) could be placed through a 5 French gauge catheter and this has advantages in small children. Where the vessels to be occluded were larger, latex balloons up to 12 mm in diameter were used. The silicone balloons are inflated with iso-osmotic contrast medium and have an extra advantage in that they may be fluid propelled. They are prepared ready for use, unlike the latex balloons which come in a kit form and have to be prepared and hand tied to the balloon catheter before use. The latex balloons are initially inflated with contrast medium to determine their position and their occluding effect. Contrast medium is then aspirated and replaced with an equal volume of a mixture of two silicone monomers. At body temperature these polymerise in about 15 minutes and then vulcanise. At this stage the process is no longer reversible. When the arteries to be occluded were small (case 6) and a detachable balloon or steel coil could not be safely inserted small particles of gelfoam (Sterispon) were injected through the catheter placed in the proximal vessel.

In the case of the pulmonary arteriovenous malfor-

mation (case 3) in which it was considered appropriate to obliterate the malformation as well as the feeding arteries, multiple steel coils were used in addition to large gelfoam fragments. In this case two embolisation procedures were required to achieve complete occlusion.

Results

In all of five cases in which detachable balloons were used to occlude major arteries complete occlusion was confirmed by angiography at the end of the procedures (Figs. 1, 2, 3, and 4). In one of these patients (case 1) coronary arteriography seven months after the embolisation confirmed permanent occlusion as well as a good postangioplasty result (Fig. 1). In the other four cases follow up clinical evaluations, supported when appropriate by radionuclide studies, confirmed that successful occlusion had persisted.

In the patient (case 3) with the pulmonary arteriovenous malformation (Fig. 5a) the initial embolisation procedure with three large steel coils was only partly successful. Despite an improvement in the arterial oxygen saturation to within the normal range, a study with radionuclide labelled microspheres showed that right to left shunting though reduced was still appreciable. A pulmonary arteriogram three months after this embolisation procedure showed that the single feeding artery was still patent (Fig. 5b).

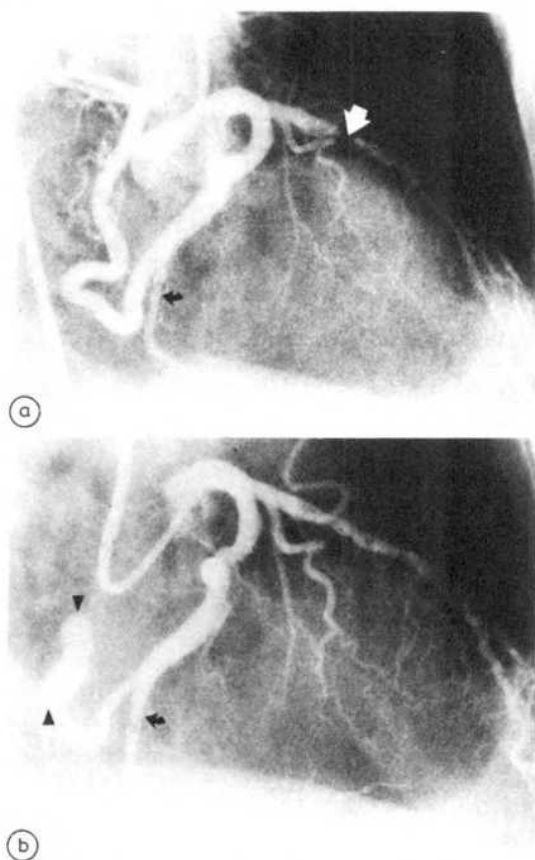


Fig. 1 (a) Left coronary arteriogram in case 1. Note the severe proximal stenosis of the anterior descending branch of the coronary artery (white arrowhead). The point of occlusion of the fistula must be distal to the last marginal branch (black arrow). (b) 7 months after embolisation and angioplasty. The balloon is filled with contrast (black arrowheads) and positioned well distal to the last marginal branch (black arrow). Good angioplasty result noted.

Complete occlusion was produced with three further steel coils and large gelfoam pieces (Fig. 5c). Subsequent radionuclide studies showed no evidence of right to left shunting. They also showed a segmental perfusion defect in the region of the occluded malformation.

The patient in whom multiple aortopulmonary collaterals were embolised with gelfoam particles showed clinical improvement, and successful occlusion of the arteries was seen angiographically (Fig. 6c). Radionuclide studies showed an appreciable decrease in the left to right shunt after the procedure.

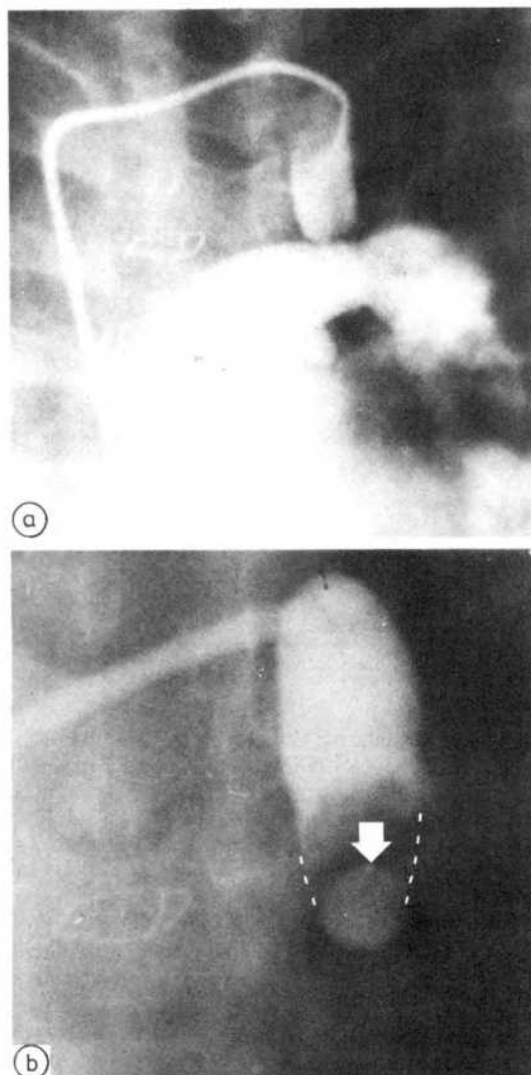


Fig. 2 (a) Injection into the Blalock-Taussig shunt (catheter via right sided aortic arch) in case 2. Note the dilatation of the subclavian artery and the stenosis where it anastomoses with the left pulmonary artery. (b) Post embolisation injection of medium into the Blalock-Taussig shunt shows occlusion and a radiolucent defect due to the silicone filled balloon. The rounded opacity is due to some residual contrast in the balloon, and the very small density area (white arrowhead) is a metal marker in the balloon.

In the patient with the left circumflex coronary artery-coronary sinus arteriovenous malformation (case 7) the flow through the circumflex coronary artery was so great that normal myocardial branches were not visualised when the aortic root or main coronary artery were injected (Fig. 4a). Only when a non-detachable balloon catheter with proximal injec-

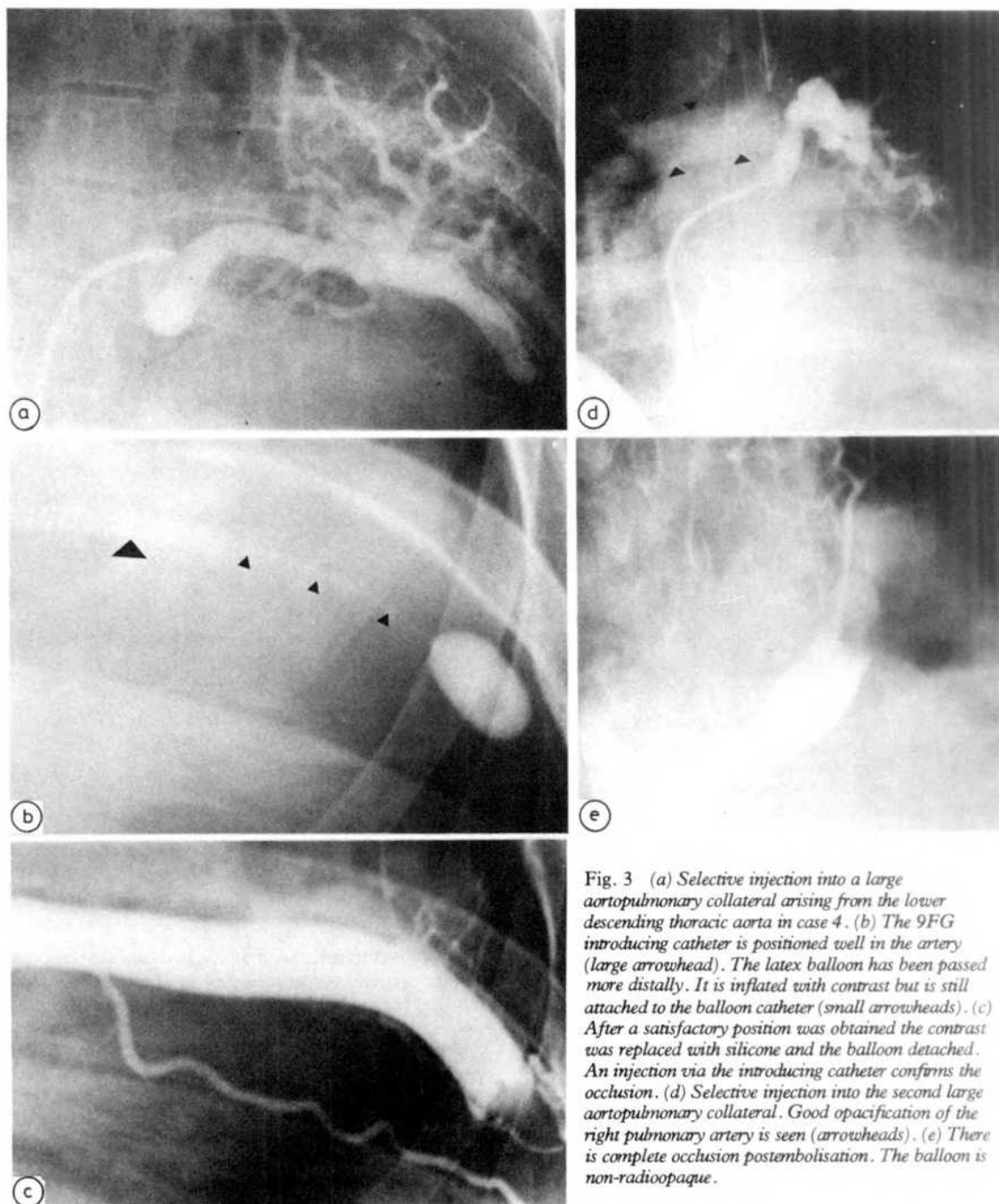


Fig. 3 (a) Selective injection into a large aortopulmonary collateral arising from the lower descending thoracic aorta in case 4. (b) The 9FG introducing catheter is positioned well in the artery (large arrowhead). The latex balloon has been passed more distally. It is inflated with contrast but is still attached to the balloon catheter (small arrowheads). (c) After a satisfactory position was obtained the contrast was replaced with silicone and the balloon detached. An injection via the introducing catheter confirms the occlusion. (d) Selective injection into the second large aortopulmonary collateral. Good opacification of the right pulmonary artery is seen (arrowheads). (e) There is complete occlusion postembolisation. The balloon is non-radioopaque.

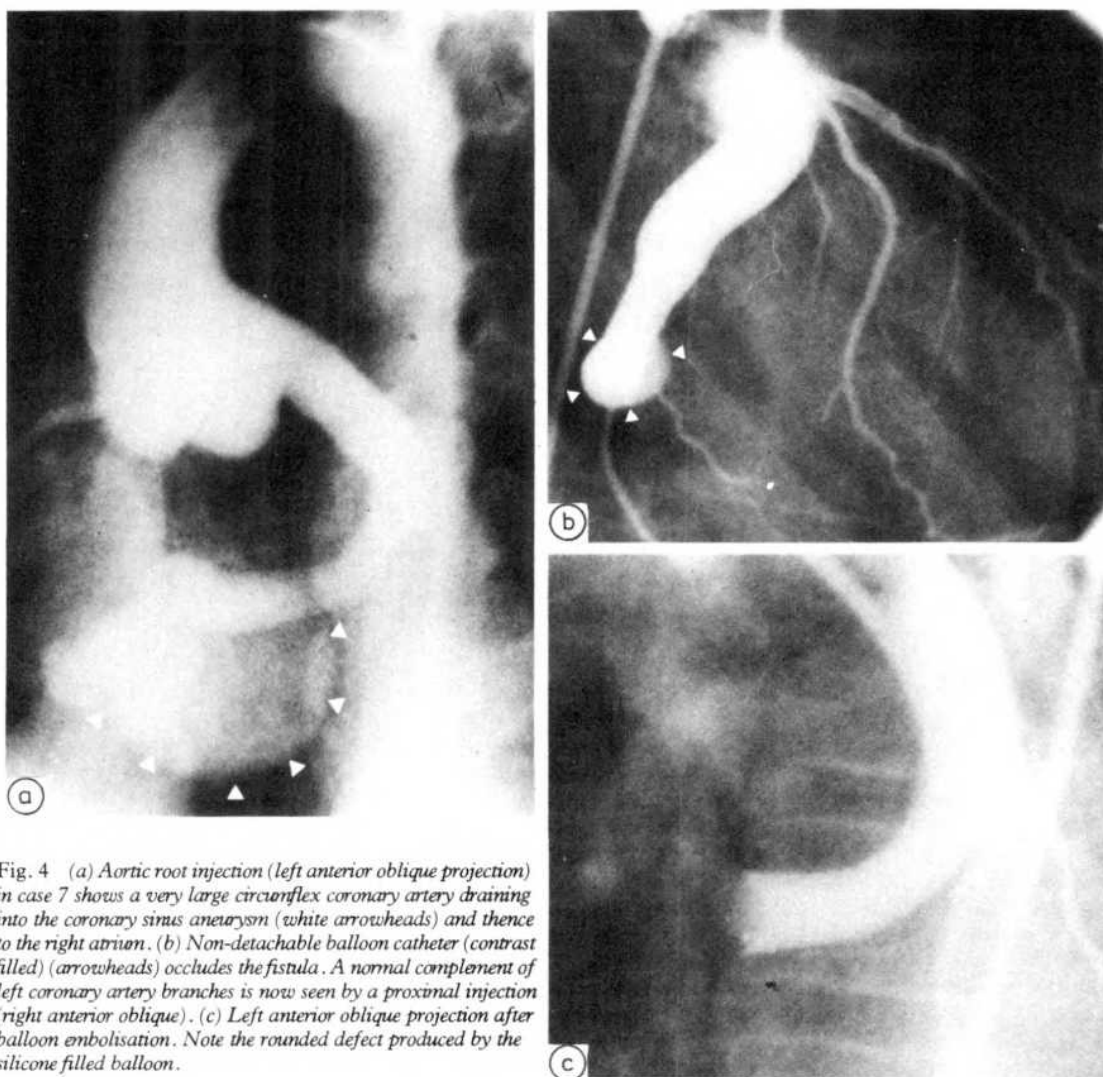


Fig. 4 (a) Aortic root injection (left anterior oblique projection) in case 7 shows a very large circumflex coronary artery draining into the coronary sinus aneurysm (white arrowheads) and thence to the right atrium. (b) Non-detachable balloon catheter (contrast filled) (arrowheads) occludes the fistula. A normal complement of left coronary artery branches is now seen by a proximal injection (right anterior oblique). (c) Left anterior oblique projection after balloon embolisation. Note the rounded defect produced by the silicone filled balloon.

tion holes was placed so that it occluded the distal artery and fistula could the normal left coronary branches be clearly demonstrated (Fig. 4b). This non-detachable balloon was left inflated for 15 minutes and produced no adverse clinical effects or ischaemic changes on the electrocardiogram. Some right bundle branch block occurred, but a month after embolisation this was no longer present. Coronary angiography after balloon embolisation confirmed occlusion of the fistula and the presence of all the normal coronary branches (Fig. 4c). A pre-embolisation thallium computed tomogram showed reversible myocardial ischaemia due to a left coronary steal, and a repeat study three months after embolisa-

tion showed that these changes had largely resolved.

The procedure was tolerated in all patients including two (cases 5 and 6) who were still receiving post-operative intensive care. None of our patients had complications attributable to embolisation. One patient died (case 5) of a cause unrelated to embolisation three weeks after the procedure. To date, the remainder are alive and well.

Two patients (cases 1 and 2) have been the subject of previous case reports.^{1 2}

Discussion

In recent years many methods of transcatheter embol-

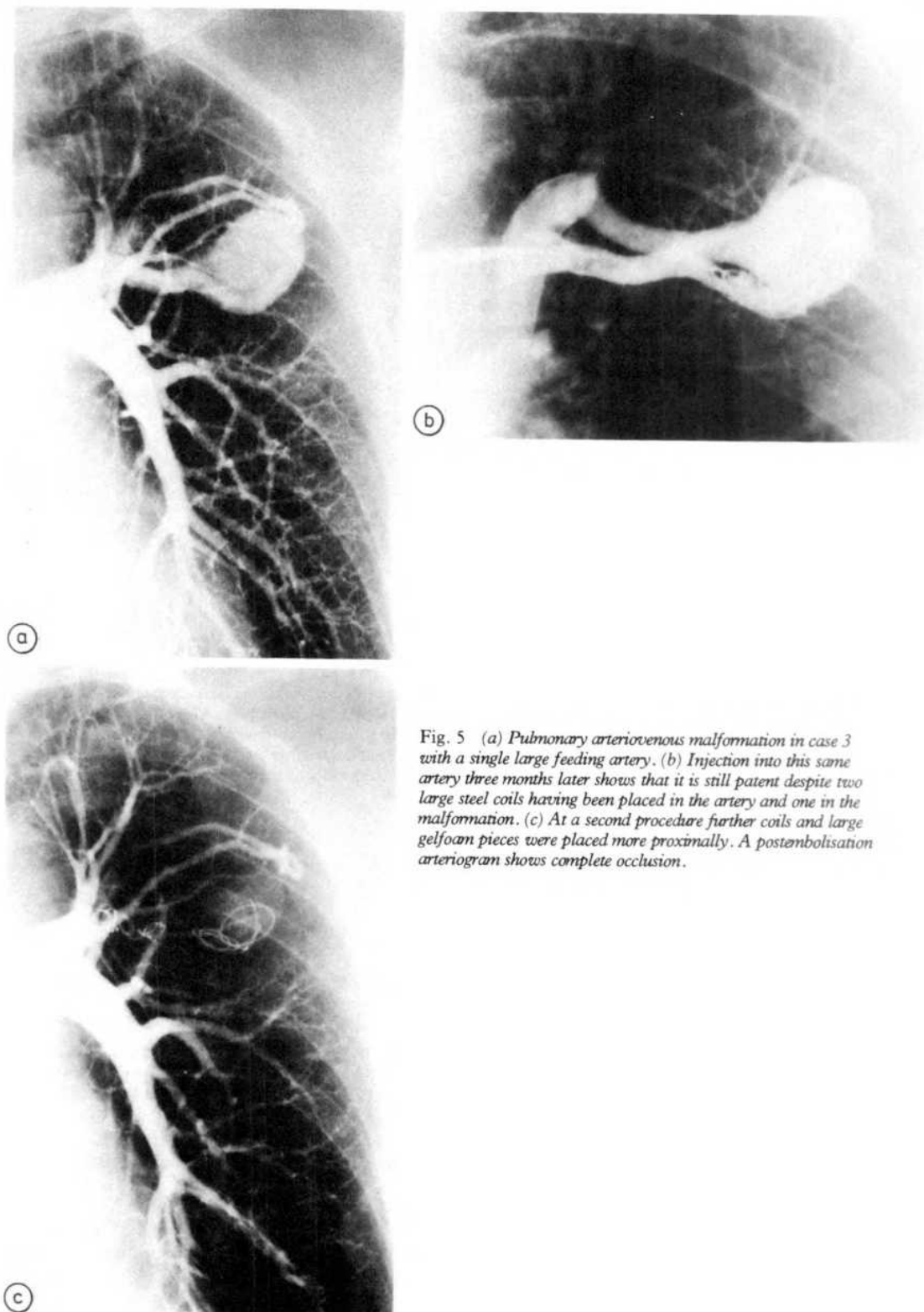


Fig. 5 (a) Pulmonary arteriovenous malformation in case 3 with a single large feeding artery. (b) Injection into this same artery three months later shows that it is still patent despite two large steel coils having been placed in the artery and one in the malformation. (c) At a second procedure further coils and large gelfoam pieces were placed more proximally. A postembolisation arteriogram shows complete occlusion.

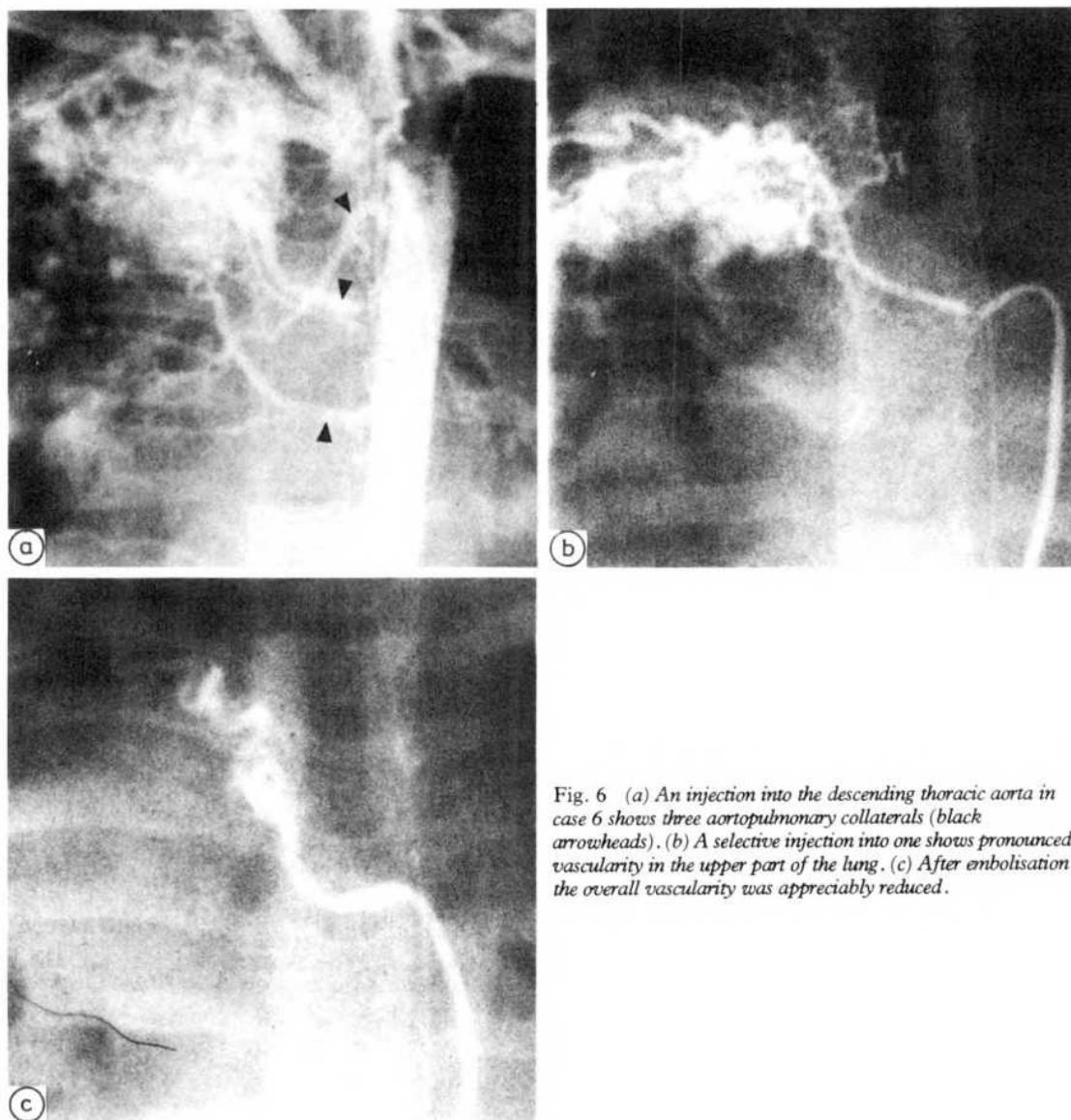


Fig. 6 (a) An injection into the descending thoracic aorta in case 6 shows three aortopulmonary collaterals (black arrowheads). (b) A selective injection into one shows pronounced vascularity in the upper part of the lung. (c) After embolisation the overall vascularity was appreciably reduced.

isation have been developed. Each has its advantages and disadvantages which must be taken into account when a decision is made on the type of procedure to use. Furthermore, the comparative risks of transcatheter embolisation and the surgical alternatives must be assessed since the clinical state of the patient and knowledge of the risks, failures, and complications of surgery will often dictate the course of action. Transcatheter occlusion of persistent ductus arteriosus was introduced more than 10 years ago,³

but it has not become generally accepted because the success rate of surgical closure is predictably high with a very low risk. Embolisation has not proved itself to be a simple and safe alternative.

The application of transcatheter embolisation in congenital cardiovascular malformation has also been limited. Occlusion of collateral arteries to the lung in tetralogy of Fallot has been reported,⁴ and more recently five assorted congenital vascular anomalies in the thorax have been embolised by means of Gian-

turco steel coils.⁵ In one case the tissue adhesive Bucrylate was used to occlude a bronchial artery before surgical repair in tetralogy of Fallot.⁶ Apart from the embolisation of pulmonary arteriovenous malformations⁷ reports generally describe experience in single cases.⁸⁻¹⁰

Our experience with this varied group of cases prompts several comments. Firstly, in skilled hands these procedures are successful and we encountered no complications. Secondly, they can be carried out even in young children. Thirdly, embolisation can be successfully performed and is well tolerated in critically ill patients.

Detachable balloon embolisation was used in five of our seven cases. Balloon embolisation has been employed in only a very small fraction of all embolisation cases and has mainly been used in intracerebral vascular malformations.¹¹ The major advantage of using detachable balloons is that they can be positioned in the vessel at the exact point where occlusion is required. Only when this position and the occluding effect have been confirmed by contrast medium injected through the introducing catheter is the balloon finally detached. Up to this time the process, unlike all other forms of embolisation, is reversible. In fistulous vascular connections and malformations with large vessels and high flow this avoids the risks of distal embolism. The high blood flow in large arteries may make them difficult to occlude completely. Detachable balloons of up to 12 mm in diameter can be used to occlude all except very large vessels. Several detachable balloon embolisation systems are available but only two were used in our patients. These balloons are biologically inert and produce permanent occlusion.

There are risks associated with the use of detachable balloons and operators must have experience in embolotherapy before attempting such procedures, especially in the heart. Difficulties with underinflation or use of too small a balloon may occur. Detachment of the balloon can then lead to pulmonary or, more seriously, systemic embolism. It may be difficult to detach silicone filled latex balloons. Alternatively premature detachment before vessel occlusion is a risk with the silicone balloons, especially in high flow arteries. Also early deflation can occur as they are filled with contrast media. Use of large introducing catheters and coaxial catheters in what may be lengthy procedures increases the risks of intravascular thromboembolic complications. These are reduced by routine heparinisation.¹²

Sometimes aortopulmonary collaterals consist of small and multiple arteries and thus are unsuitable for balloon embolisation. The precise site of embolisation in these end arteries, however, is not critical, and simpler embolisation materials can be used in such

vessels. Radiologists have for many years been embolising hypertrophied bronchial and intercostal arteries in patients who have severe haemoptysis and chronic lung disease. Usually particulate emboli such as the biodegradable Sterispon have been used, although liquid embolic agents (alcohol, cyanoacrylate) have sometimes been advocated. Rarely a bronchial or intercostal artery also gives rise to a spinal medullary branch and spinal cord damage may be a complication of such embolisations.¹³ Before embolisation is considered, careful selective arteriograms (cut film is better than cine film) are essential. The presence of an anterior spinal artery arising from an intercostal/bronchial aortopulmonary collateral is an absolute contraindication to embolisation. With a careful approach and use of particulate rather than liquid emboli the risks appear to be very low. Of 104 patients who have had embolisation of bronchial and non-bronchial arteries for massive haemoptysis there were no medullary complications reported.¹⁴ Care must also be taken to avoid the more general complications of embolisation such as reflux of emboli and embolisation of distal aortic branches.

Multiple steel coils and large pieces of gelfoam were used to occlude the large pulmonary arteriovenous malformation. Though this was successful it took two procedures to occlude the vessel completely. Though others have used coils successfully to occlude pulmonary arteriovenous malformations, use of a single detachable balloon would probably have been as effective and perhaps more appropriate.

Only three of our seven patients had not previously had cardiac surgery. The other four cases all had complex congenital heart disease and had surgery on at least two occasions. In all four cases further surgery would have been necessary in the absence of an alternative embolisation technique. Two patients (cases 5 and 6) were regarded as poor surgical risks. In all our cases the aim of the embolisation was achieved and there were no complications related to the procedure.

Although the indications for these procedures are limited, there is scope for the extension of their use. For example, catheter embolisation of systemic to pulmonary collaterals in patients with multifocal blood supply can be performed. In the controlled environment of the catheter laboratory, trial reversible occlusions controlled by radioisotope imaging of the distribution of pulmonary perfusion¹⁵ could provide the ideal method of differentiating those collaterals which it is safe to occlude from those which it is not.

Our results strongly suggest that in skilled hands transcatheter embolisation is a safe and effective treatment of certain congenital cardiovascular malformations. Embolisation can be performed in critically ill children, and when vascular access is available

it can be repeated when necessary. Embolisation procedures should be useful techniques complementary to surgery, and may in some instances obviate the need for operation.

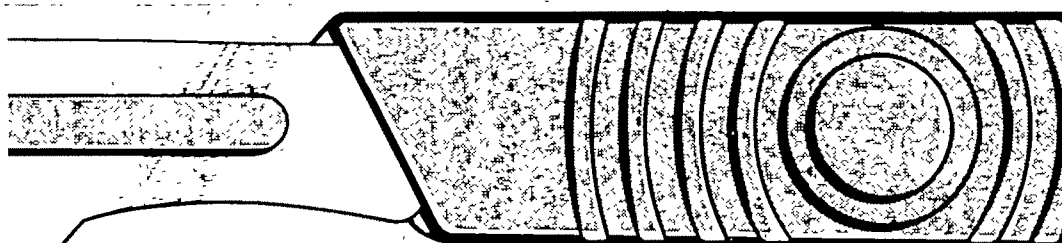
We thank Dr J S Staffurth, Dr E Sowton, Mr P B Deverall, and Mr J C Lincoln for permission to report details of some of these cases.

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Functional and anatomical correlates in atrial septal defect

An echocardiographic analysis

J COLIN FORFAR,* MICHAEL J GODMAN

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SUMMARY The results of cross sectional echocardiography, intracardiac contrast echocardiography, and balloon sizing techniques and conventional haemodynamic assessment were correlated in 40 consecutive patients evaluated for an isolated left to right shunt at atrial level. Echo free areas along the septum were identified in 23 of 25 patients with a secundum defect, but not in two with a fenestrated defect, and in the upper atrial septum in three of four patients with a sinus venosus defect. No false positive results occurred in 11 patients with a probe patent foramen ovale. Saline contrast injection into the left atrium showed significant left to right shunting in all patients with atrial septal defect; inferior vena caval injection produced right to left shunting in 15 of 29 patients and a negative contrast effect in eight of 29 patients with an atrial septal defect, although neither correlated quantitatively with defect diameter or magnitude of the left to right shunt.

Echocardiographic assessment of defect size as small, moderate, or large showed a highly significant correlation with balloon measurement of defect diameter, although some overlap between the groups was evident. In contrast, the correlation between defect diameter and pulmonary to systemic blood flow ratio was poor, mainly because of highly variable shunting in patients with an anatomically large defect.

Cross sectional echocardiography has high sensitivity and specificity in the diagnosis of the non-fenestrated atrial septal defect and provides quantitative information about defect diameter. Contrast studies do not add to the diagnostic value of imaging from the subcostal position. The poor correlation between defect size and the measured shunt suggests that the latter may not be the best criterion for surgical management and that size could be an important factor likely to influence both the long term prognosis and the decision for closure.

The decision to close defects of the interatrial septum in younger patients conventionally rests on the extent of intracardiac shunting assessed by oximetry. Although there is little debate about the management of patients with a high pulmonary blood flow and right ventricular enlargement, the relation between flow and defect size with a small or modest overall

shunt without specific chamber enlargement is less well understood and the decision for closure is less clear cut.¹

The diagnostic value of cross sectional echocardiography in identifying atrial septal defects has been recognised,²⁻⁵ although the place of contrast echocardiography as a diagnostic aid remains uncertain.⁶⁻⁸

The purpose of this study was to assess the sensitivity and specificity of cross sectional echocardiography in the diagnosis and quantitative evaluation of atrial septal defects and to examine the relation between defect size and the extent of interatrial shunting, the latter measured conventionally by oximetry and directly by intracardiac contrast echocardiography.

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Accepted for publication 22 March 1985

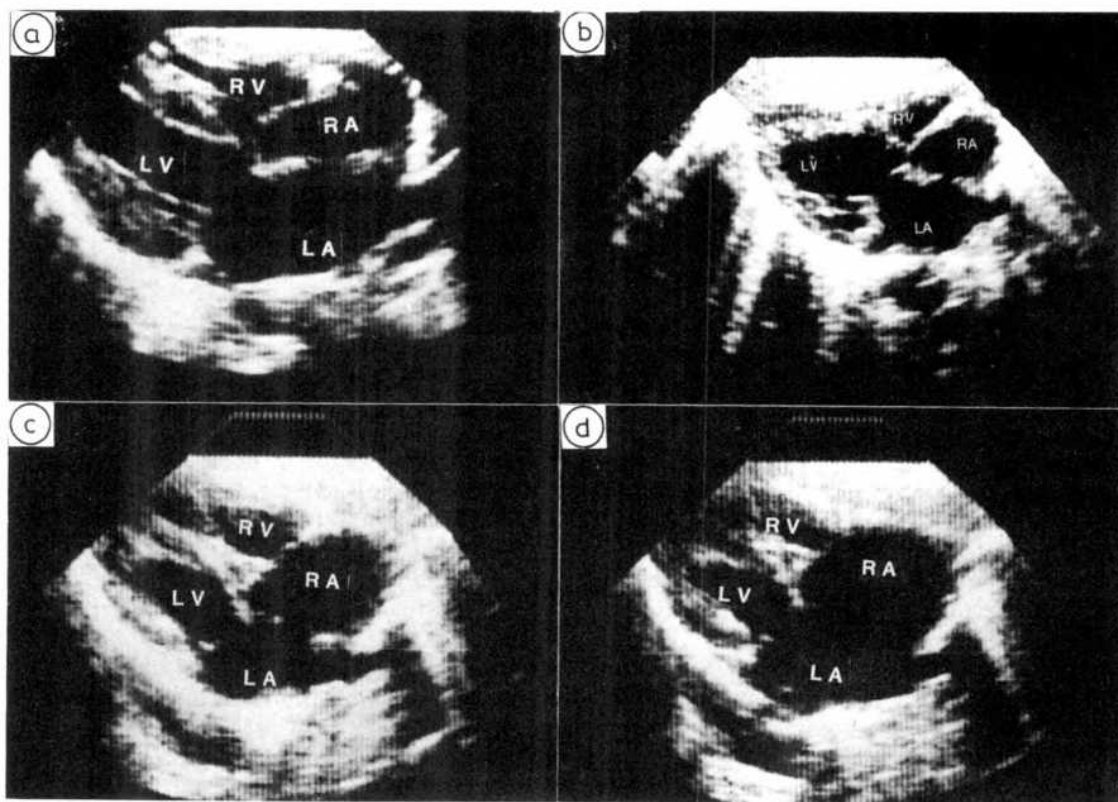


Fig. 1 Echocardiographic grading of the atrial septum from the subcostal position as intact (a), or showing a small (b), moderate (c), or large (d) defect.

Patients and methods

Forty consecutive patients (19 boys, 21 girls; aged 1–16 years) were studied over a 21 month period at the time of cardiac catheterisation for evaluation of a possible isolated left to right shunt at atrial level. Patients in whom an ostium primum defect was suspected, those with additional cardiac malformations, or those with a calculated pulmonary vascularity resistance in excess of 4 units were excluded from the analysis. After all of the investigative procedures, 25 patients were categorised as having a secundum defect, four a sinus venosus defect, and 11 a probe patent foramen ovale without evidence of intracardiac shunting.

ECHOCARDIOGRAPHY

After clinical evaluation, including echocardiography and chest radiography, each patient underwent an echocardiographic examination before cardiac catheterisation. Cross sectional studies of the inter-atrial septum were performed from the subcostal and

the apical four chamber view using an ATL Advanced 850 mechanical sector scanner with 3 or 5 MHz transducers or Kontron Irex Mark III phased array scanner. The septum was classified as intact (0) or showing a small (+), moderate (++), or large (+++) defect where 30%, 30–60%, or >60% of total septal length respectively appeared to be free of echoes (Fig. 1).

Contrast echocardiographic studies were performed from the left atrium and inferior vena cava at the time of diagnostic catheterisation. Saline injections (2–4 ml) were repeated if necessary until dense opacification of the chamber was achieved. Injection into the left atrium allowed classification of the left to right shunt as small (+), moderate (++), or large (+++) according to whether opacification within the atrium and ventricle was minimal, less than, or equal to opacification of the left sided chambers. Injection into the inferior vena cava established the presence or absence of right to left shunting at atrial level (Fig. 2a) or a negative contrast effect where filling of the right atrium by non-opacified blood from the left

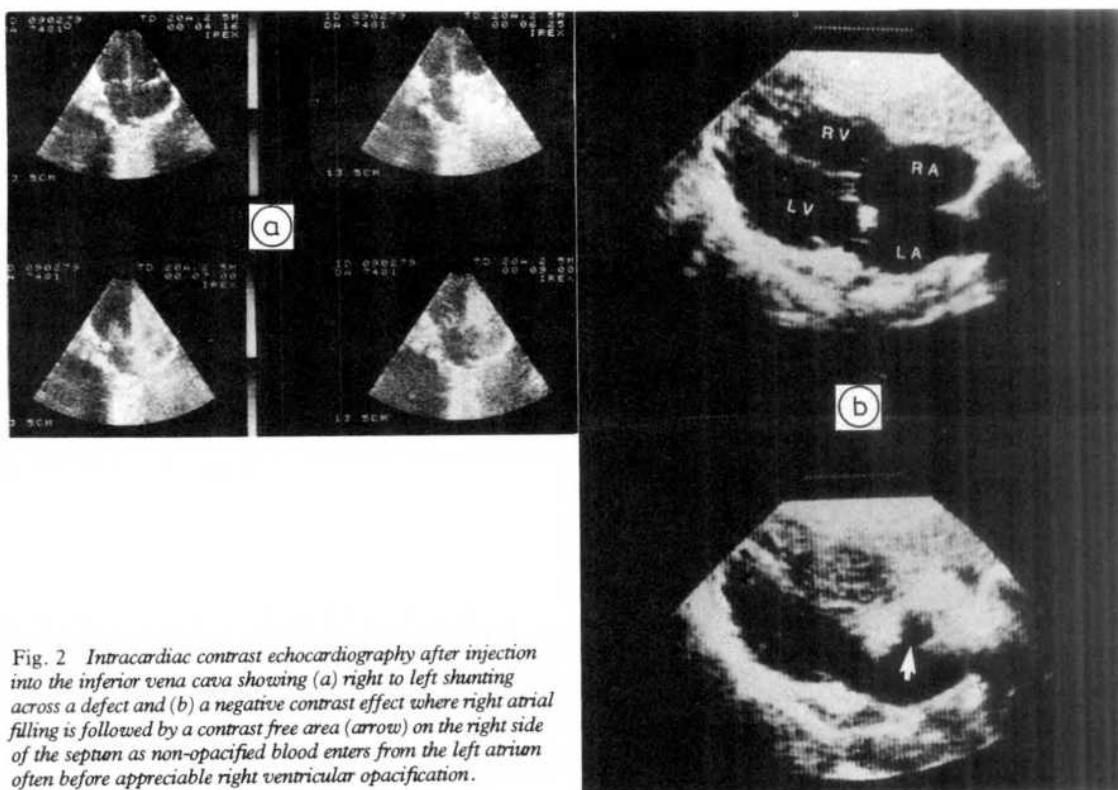


Fig. 2 Intracardiac contrast echocardiography after injection into the inferior vena cava showing (a) right to left shunting across a defect and (b) a negative contrast effect where right atrial filling is followed by a contrast free area (arrow) on the right side of the septum as non-opacified blood enters from the left atrium often before appreciable right ventricular opacification.

atrium resulted in a contrast free area on the right side of the septum at the level of the defect, often before significant right ventricular opacification occurred (Fig. 2b).

HAEMODYNAMIC MEASUREMENTS

Routine cardiac catheterisation was performed from the saphenous vein under light ketamine anaesthesia. The atrial septum was crossed in all patients except one with a high sinus venosus defect. Arterial oxygen saturation was equated with a sample from the left ventricle or femoral artery and mixed venous saturation derived from superior (SVC) and high inferior (IVC) vena cava saturation according to the formula⁹: mixed venous saturation (%) = (3SVC + HIVC)/4 saturation (%). The pulmonary systemic blood flow ratio was derived from standard options.

BALLOON SIZING TECHNIQUE

Measurement of defect diameter was achieved using a balloon catheter according to the method of King *et al.*¹⁰ A Fogarty 8–8F, 8–10F, or 8–14F embolectomy catheter (Edwards Laboratories, Santa Ana, California) was advanced into the left atrium and drawn

across the defect into the right atrium with increasing volumes of dilute contrast until resistance was felt and the balloon remained in the left atrium (Fig. 3a). The maximum volume in the balloon that allowed the defect to be crossed was noted. The defect diameter was derived by inflation of the balloon to exactly the same volume and directly measured using a series of calibrated aluminium templates (Fig. 3b). Reproducibility studies by the same observer showed a maximum variability in defect diameter in eight patients (measured twice during catheterisation) of 2 mm. Technically satisfactory sizing of a secundum defect was achieved in all except one patient, in whom the 8–14F catheter proved too large for the saphenous vein; maximum balloon diameter with 8–10F catheter was 24 mm. Sizing was possible in only two of four patients with a sinus venosus defect. As preliminary studies, in agreement with King *et al.*¹⁰ had found a large margin of safety between the manufacturer's recommended maximum liquid capacity for the balloon and the volume at which the balloon rupture occurred (with a minimum rupture volume three times the recommended maximum inflation volume) the maximal liquid capacity was exceeded by up to

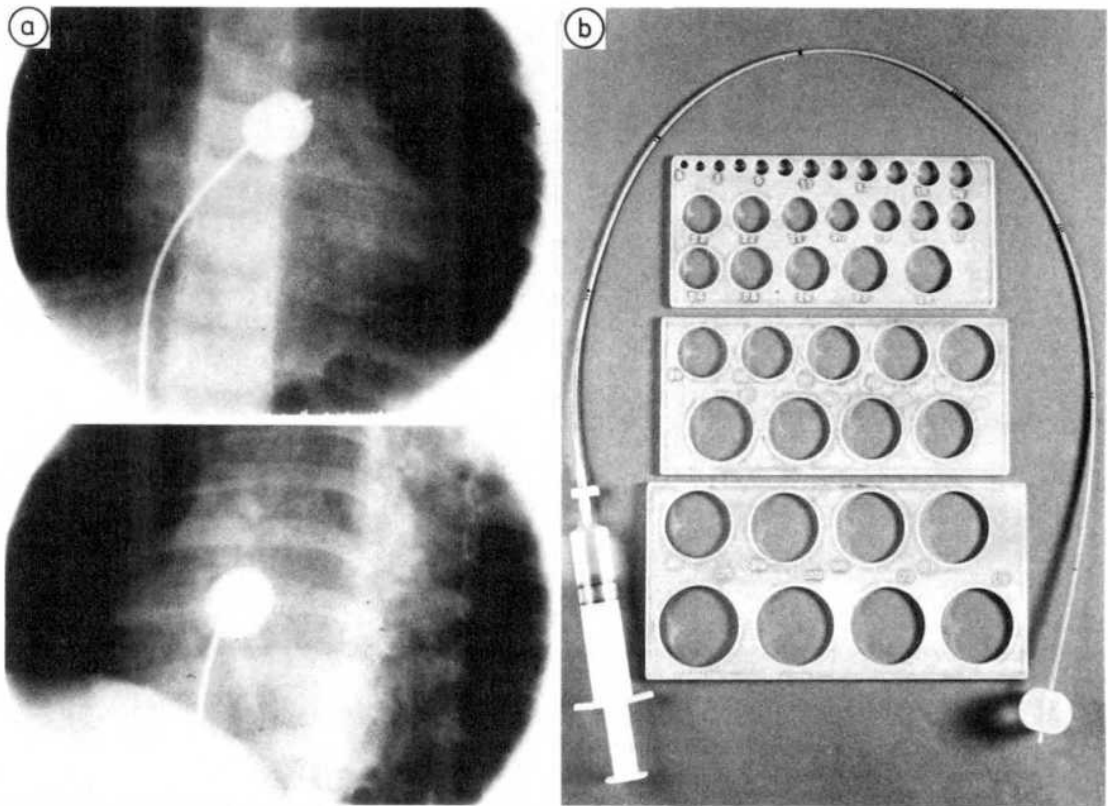


Fig. 3 (a) Angiograms showing balloon sizing of defect diameter from anteroposterior (top) and left oblique projection (below). The contrast filled balloon lies across a secundum defect and the maximum volume needed to cross the defect is noted and the diameter at that volume derived using a series of calibrated templates (b).

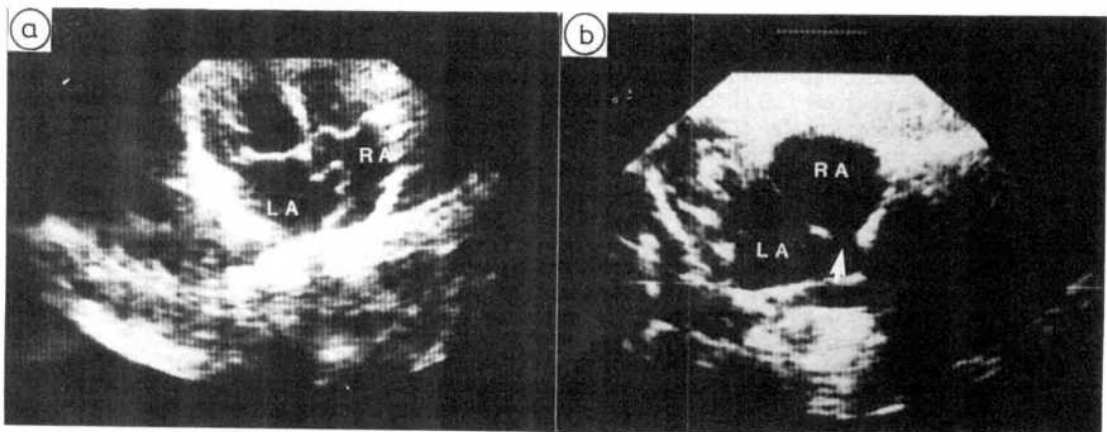


Fig. 4 Echocardiograms showing (a) an aneurysm of the intra-atrial septum protruding into the right atrium. The aneurysm was associated with a large fenestrated septal defect, although no echo free areas are seen. (b) A sinus venosus defect produced an echo free area (arrow) in the upper atrial septum.

Table Contrast echocardiographic assessment of atrial shunting and negative contrast effect in patients with atrial septal defect and patent foramen ovale

	No of patients	No with left-right shunt	No with right-left shunt	No with negative contrast
Atrial septal defect:				
Secundum	25	25	14	8
Sinus venosus	4	3*	1	0
Patent foramen ovale	11	5	0	0

*Defect not crossed in one patient.

50% before a change was made to a catheter with a larger balloon. No complications of the procedure were noted. The inflated balloon floated into and wedged in the main pulmonary artery in two patients but was rapidly deflated without any apparent adverse haemodynamic effect or arrhythmia.

SURGICAL ASSESSMENT

Further assessment of defect diameter at the time of closure on cardiopulmonary bypass was available in 22 patients. For the purposes of comparison with the balloon sizing technique, the shape of the defect was noted and its area carefully measured. In those patients with non-circular defects, a diameter giving an area equivalent to that measured at the time of operation was used for comparison with the balloon sizing technique.

STATISTICAL ANALYSIS

The relation between echocardiographic assessment of defect size and balloon size or pulmonary blood flow was analysed by analysis of variance. Balloon and surgical assessment of defect size was correlated with balloon size and pulmonary blood flow using a linear regression coefficient with least squares method of analysis.

Results

DIRECT ECHOCARDIOGRAPHY

Echo free areas were seen along the atrial septum in 23 of 25 (92%) patients with a secundum defect, but not in two patients, both of whom had a fenestrated defect (one of which occurred in association with a septal aneurysm) (Fig. 4a). Echocardiography also identi-

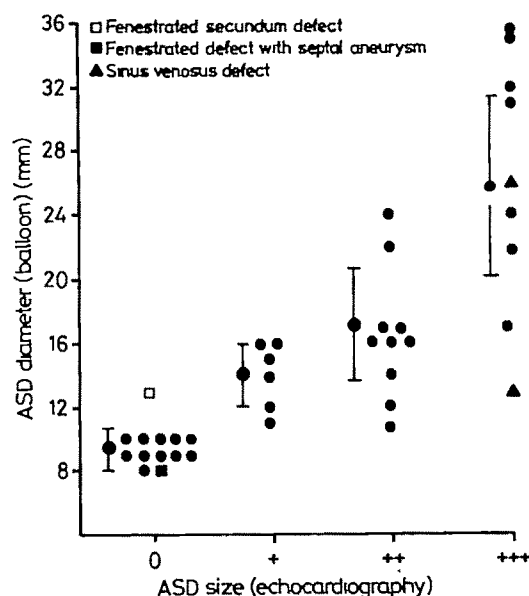


Fig. 5 Diameter of atrial septal defect (ASD) by echocardiography and balloon sizing techniques ($n=38$). Mean (SD) values are shown. 0, intact; +, small; ++, moderate; +++, large.

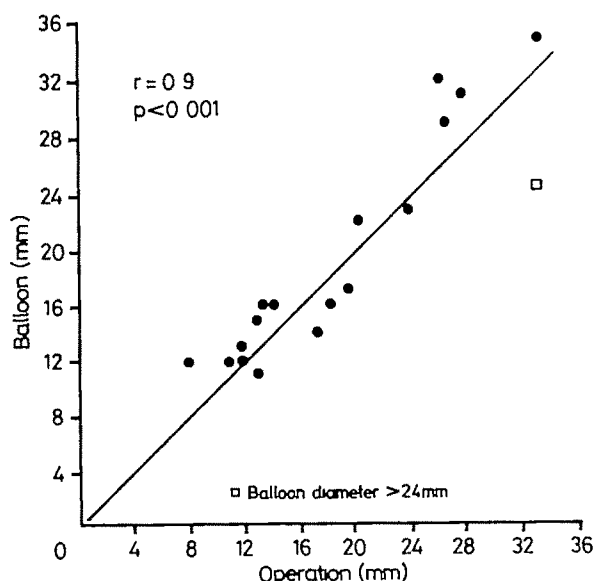


Fig. 6 Comparison of atrial septal defect diameter measured directly at operation and indirectly by balloon sizing techniques ($n=18$).

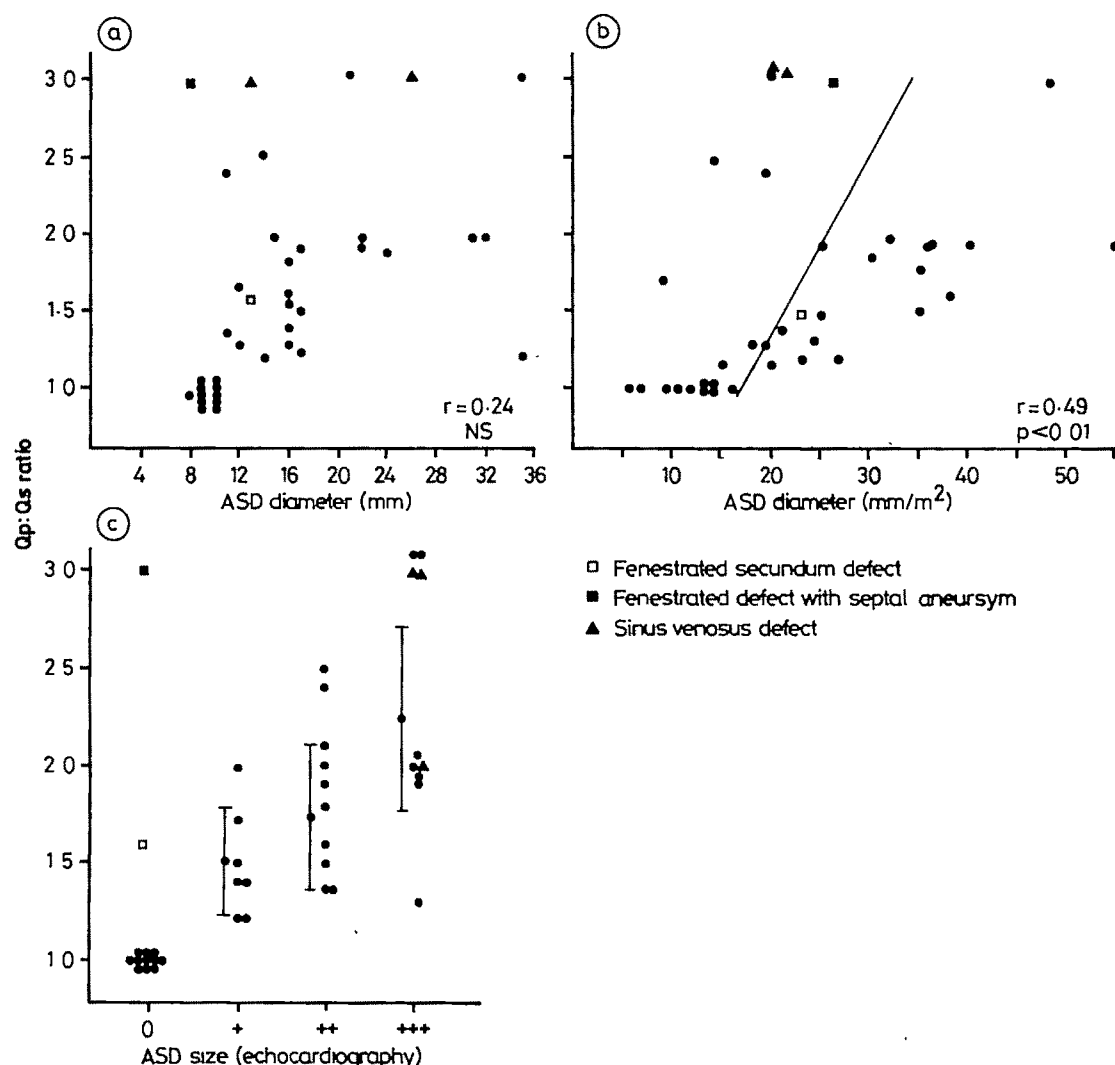


Fig. 7 Relation of pulmonary to systemic blood flow ratio ($Q_p:Q_s$) to size of atrial septal defect estimated by (a) balloon diameter ($n=38$), (b) balloon diameter indexed to body surface area ($n=38$), and (c) echocardiography ($n=40$). 0, no shunt; +, small; ++, medium; +++, large.

fied echo free areas in the upper atrial septum in three of four patients with a sinus venosus defect (Fig. 4b), but the defect was not visualised in the fourth patient. Although thinning of the septum at the level of the fossa ovalis was observed in most of the 11 patients with a foramen ovale, echo free areas along the septum were not seen.

CONTRAST ECHOCARDIOGRAPHY

Contrast injection into the left atrium showed variable left to right shunting in all of the 28 patients with an atrial septal defect in whom the defect was crossed

(one sinus venosus defect not crossed). A small amount of left to right shunting, probably catheter related, was also present in five of the 11 patients with a foramen ovale. Right to left shunting at atrial level was detected in 15 of 29 patients and a negative contrast effect in eight of 29 patients with an atrial septal defect, but neither was seen in patients with a foramen ovale. The Table summarises these results.

SIZING TECHNIQUES

The echocardiographic grading of defect size as small, moderate, or large showed a fairly close and highly

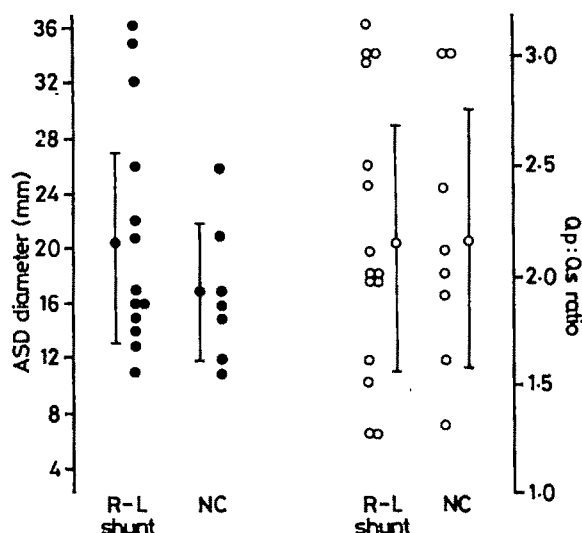


Fig. 8 Balloon assessment of atrial septal defect (ASD) diameter (●) and pulmonary to systemic blood flow ratio (Qp:Qs) (○) in patients in whom a right to left (R-L) shunt or negative contrast (NC) effect was seen.

significant ($p < 0.005$) relation to the diameter measured by the balloon, although some overlap between the groups was evident (Fig. 5). The balloon technique did not distinguish between defects of < 10 mm in diameter and a foramen ovale, but this has little practical significance as all the defects correctly identified by echocardiography had a diameter of ≥ 11 mm. In both patients with a fenestrated secundum defect, the balloon substantially underestimated overall defect size.

Of the 18 patients in this series who had undergone operative closure of a simple non-fenestrated secundum defect, comparison of defect diameter measured at operation with that at catheterisation showed a close correlation with no tendency for either measurement to vary systematically with respect to the other (Fig. 6).

RELATION BETWEEN DEFECT SIZE AND SHUNT

In contrast, the relation between defect size and pulmonary to systemic blood flow ratio at the time of catheterisation was poor (Fig. 7a). No correlation was evident unless defect diameter was indexed to body surface area, when the correlation did achieve statistical significance (Fig. 7b). In patients with large defects (> 25 mm in diameter) the ratio of pulmonary to systemic blood flow varied from 1.3 to 3.1. A similar variability in defect diameter was present in patients with a large left to right shunt, although for anatomical reasons, either because of fenestration or position high in the septum, the accuracy of balloon

sizing was limited in some of these patients. Variability in the measured shunt was particularly pronounced in patients with a large (+++) defect on echocardiography (Fig. 7c). The mean left to right shunt in seven patients with a small (+) defect was 1.5:1 and the maximum shunt 2.0:1.

The presence of a right to left shunt or negative contrast effect did not allow prediction of either the size or the magnitude of the intracardiac shunt in patients with an atrial septal defect (Fig. 8), both measurements showing considerable variability in the patients with these contrast phenomena.

Discussion

This study has validated cross sectional echocardiography in children as a sensitive and specific investigation for the diagnosis and quantitative evaluation of isolated defects of the atrial septum with two exceptions. Firstly, fenestrated secundum defects (present in 2 of 25 (7%) patients with atrial septal defect in this series) may be missed on echocardiography, and, secondly, the sensitivity of diagnosis of defects of the upper atrial septum remains in some doubt for in this series a sinus venosus defect was not visualised in one out of four patients in whom it was present. It is not surprising considering the anatomy of fenestrated defects that they can be missed by cross sectional echocardiography, but the recognition of an atrial aneurysm or an increased right ventricular dimension with paradoxical septal motion on M mode recording should prompt consideration of this diagnosis. M mode echocardiographic findings compatible with right ventricular volume overloading in the presence of an intact fossa ovalis by cross sectional echocardiography should also alert the examiner to examine the upper atrial septum and pulmonary venous drainage with care, particularly if the clinical findings have suggested an atrial septal defect.

Although minute degrees of right to left shunting have been detected in children with uncomplicated ostium secundum defects,¹¹ we found that despite dense right atrial opacification from central injection of contrast medium right to left shunting was present in no more than 50% of children. Furthermore, the range of defect size and pulmonary to systemic blood flow ratios in patients with echocardiographically demonstrated right to left shunting was considerable (Fig. 8) and too large to allow classification of the defect likely to be associated with this type of shunt. This observation does not accord with that of Fraker *et al*, who noted right to left shunting in all of 11 adult patients with an atrial septal defect, seven of whom had no right to left shunt detectable by oximetry.⁶ Technical factors or changes in right atrial or right

ventricular compliance with age may explain this difference.

A negative contrast effect was present in 28% (8/29) of patients in our series, a figure considerably lower than that reported by Weyman *et al* in a study of 12 patients with atrial septal defect and a mean age of 31 years⁷ but somewhat similar to that reported by Koilpillai *et al* in 50 consecutive patients.¹² Although demonstration of right to left shunting or negative contrast effect may have a place in the differentiation of the smaller defect from thinning of the septum in the region of the fossa ovalis, we do not believe that in children contrast studies contribute significantly to the diagnostic value of imaging from the subcostal position.

The ability of balloon sizing techniques to predict accurately the diameter of defects has been established in this study for the uncomplicated secundum defect by comparison with measurements obtained during defect closure on cardiopulmonary bypass. For technical reasons the procedure cannot reliably determine the size of a sinus venosus or fenestrated secundum defect. Balloon sizing has, however, provided an anatomical measurement that can be conveniently used as a reference for validation of echocardiographic techniques and has confirmed that the extent of echo free areas defined on echocardiography from the subcostal position does indeed correspond to the margins of the septal defect itself. Echocardiography may thus have particular value in longitudinal studies of the natural history of the smaller defect that is not closed surgically¹³ and may provide information about which type of defects can undergo a spontaneous reduction in size.¹⁴⁻¹⁶

The poor correlation between defect diameter and pulmonary to systemic blood flow ratio (Fig. 7a and b) raises doubts about the use of the latter measurement as the principal basis for surgical closure. In particular, in one patient with an anatomically large defect (34 mm in diameter) the measured left to right shunt was only 1.3:1. Measurement of interatrial shunting by oximetry in the artificial environment of the catheterisation laboratory provides only a crude index of the overall shunt. Changes in ventricular compliance and vascular resistance, for example on exercise, may substantially influence interatrial blood flow.

On the other hand, echocardiographic assessment of defect size is independent of such influences and may provide important information that should influence the long term prognosis and hence the decision for closure. With typical clinical, radiographic, electrocardiographic, and echocardiographic features, routine cardiac catheterisation for the uncomplicated

moderate or large secundum atrial septal defect is unnecessary.

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Left ventricular outflow tract obstruction in complete transposition of the great arteries with intact ventricular septum

A cross sectional echocardiography study

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SUMMARY The roles of posterior bulging of the interventricular septum (septal bulge) and of systolic septal mitral apposition in patients with simple transposition of the great arteries are not known. Cross sectional echocardiograms of 40 such patients were reviewed (after exclusion of those with fixed left ventricular outflow tract obstruction) and haemodynamic findings were compared with long and short axis measurements within the left ventricle. There was no significant correlation between the degree of septal bulge and systolic gradient across the left ventricular outflow tract, but septal bulge correlated weakly with systolic right ventricular pressure and inversely with pulmonary arteriolar resistance index. Systolic left ventricular outflow gradient was inversely related to the minimum systolic distance between the anterior mitral leaflet and interventricular septum. No patients without complete systolic apposition of the anterior mitral leaflet and interventricular septum had a left ventricular outflow gradient >20 mm Hg. Conversely, even when cross sectional echocardiography showed apparently total obstruction of the left ventricular outflow tract at some time in systole there was often no significant gradient detected during haemodynamic study. In the short axis cuts closeness of the papillary muscles to the interventricular septum or to each other was unrelated to systolic gradient. This study shows that (a) cross sectional echocardiography can identify fixed obstruction of the left ventricular outflow tract in simple transposition of the great arteries; (b) the degree of septal bulge, unless complicated by fibrous thickening of the anterior mitral leaflet and interventricular septum, is unrelated to the gradient across the left ventricular outflow tract; (c) the absence of systolic septal/mitral apposition excludes a significant gradient at that site across the left ventricular outflow tract; and (d) papillary muscle geometry is unrelated to dynamic gradients across the left ventricular outflow tract in this condition.

Left ventricular outflow tract obstruction is a common accompaniment of complete transposition of the great vessels. Whereas this additional defect is beneficial in the untreated condition,¹ it complicates repair of the transposition, whether this is by transposition of venous inflow or switching of the great arteries.

It has long been recognised that the anatomical bases for left ventricular outflow tract obstruction differ greatly in patients with and without an associated

ventricular septal defect.² When a ventricular septal defect is present the varieties of left ventricular outflow tract obstruction are diverse but well understood and easily recognised by angiocardiology. By contrast the genesis of left ventricular outflow tract obstruction when the ventricular septum is intact remains undetermined.

Certain forms of left ventricular outflow tract obstruction with intact ventricular septum are anatomically easily recognisable. These include pulmonary valve stenosis, which is rare, membranous subpulmonary stenosis (analogous to discrete membranous subaortic stenosis), which is located within a few millimetres of the pulmonary valve, and anomalous

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Accepted for publication 7 May 1985

attachment of the mitral valve to the ventricular septum (clockwise rotation of the mitral valve).^{3,4} All of these are much less common than posterior septal bulge. Shaher and colleagues recognised that in transposition of the great vessels with intact ventricular septum there was a tendency for the ventricular septum to bulge into the left ventricle (septal bulge)²; this was originally attributed to septal hypertrophy. Yacoub and colleagues showed that when left ventricular pressure rose after the pulmonary trunk had been banded in preparation for an arterial switch operation, the septal bulge became much less prominent.⁵

It has been suggested, however, that septal bulge itself causes left ventricular outflow tract obstruction in some patients.⁶ In certain cases there is also a discrete line of endocardial thickening on the crest of the bulge, corresponding to the point at which the free edge of the anterior mitral leaflet would be expected to come into contact with the ventricular septum at some stage in the cardiac cycle.⁶⁻⁸ The precise relation between septal bulge and left ventricular outflow tract obstruction in simple complete transposition remains unknown.

Cross sectional echocardiography seems to be an ideal method of investigating this situation, especially since it not only yields haemodynamic information about septal bulge and motion of the anterior leaflet of the mitral valve (particularly in parasternal and apical long axis views of the left ventricle) but also demonstrates the mitral papillary muscles and chordae tendinae.⁹ The technique should be able to display subpulmonary diaphragmatic obstruction with the same accuracy as it does subaortic obstruction,¹⁰ although Daskalopoulos and colleagues were unable consistently to identify the exact site of subpulmonary obstruction in a mixed group of patients who had transposition with and without ventricular septal defects.¹¹

Since left ventricular outflow tract obstruction can result from insertion of the mitral valve into the ventricular septum itself,¹² it is also possible that obstruction may result when the papillary muscles are inserted into the free wall of the left ventricle but unusually close to the interventricular septum. Furthermore, a recent postmortem study suggested that the angle between the great vessels may be related to the systolic gradient between the left ventricle and pulmonary trunk by virtue of the degree of wedging of the posterior great vessel in the left ventricular outflow tract.¹³ Cross sectional echocardiography was proposed as an ideal way of further testing this hypothesis.

We therefore undertook this study to attempt to answer the following questions. Firstly, could cross sectional echocardiography be used to identify fixed abnormalities in the mitral valve or its tension

apparatus, in the left ventricular outflow tract, or in the pulmonary valve which cause an important systolic gradient between left ventricle and pulmonary trunk? Secondly, we wanted to determine whether there was a relation between the degree of septal bulge or the minimum systolic distance between the anterior mitral leaflet and the ventricular septum and peak gradient from left ventricle to pulmonary trunk that might be useful clinically. Thirdly, we wanted to ascertain whether there was a correlation between the relation of the papillary muscles to each other or to the ventricular septum and the peak systolic gradient from left ventricle to pulmonary trunk. Finally, was great vessel angle related to systolic gradient from left ventricle to pulmonary trunk?

Patients and methods

From March 1980 to June 1984, 79 patients at this hospital underwent cross sectional echocardiography and cardiac catheterisation for investigation of simple transposition of the great vessels. Cross sectional echocardiograms were performed by means of an Advanced Technology Laboratory mark V mechanical sector scanner with a 3.5 or 5.0 MHz transducer. Studies were stored on three quarter inch Sony tape and reviewed on a Sony PS5300 playback system. Cardiac catheterisation was performed by standard techniques, but oxygen uptake was not routinely measured. Oxygen consumption was, however, estimated¹⁴ and incorporated into the Fick equation for flow and subsequent resistance calculations.

All the echocardiograms were retrospectively reviewed in ignorance of the haemodynamic results, and still frame Polaroid photographs were taken of the left ventricle at end systole in the parasternal long axis cut (Fig. 1) and in the parasternal short axis cut (Fig. 2). The short axis pictures were taken at any stage in the cardiac cycle at which the mitral papillary muscles were clearly visible (at end diastole where possible).

The relation of the great vessels to each other was expressed as an angle (Fig. 3) measured from still frame Polaroid photographs in the parasternal short axis cut. Ratios derived from the measurements of the left ventricle were compared with haemodynamic measurements. Those patients regarded by two observers to have a fixed (see Results) abnormality of the left ventricular outflow tract or pulmonary valve on cross sectional echocardiography were excluded from further analysis.

The ratios $c:(a+b)$ and $c:g$ were taken as measures of the degree of septal bulge and $a:(a+b)$ as a measure of the eccentricity of septal bulge in the long axis cuts (Fig. 1). The ratio $d:g$ was taken as a measure of the closeness of the anterior mitral leaflet to the interventricular septum at end systole (d) compared with the

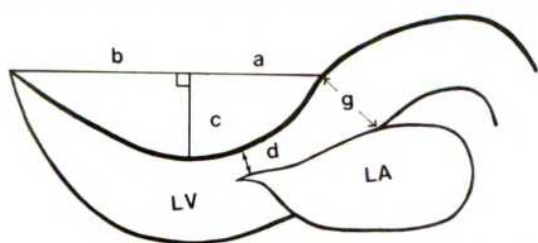


Fig. 1 Diagrammatic representation of parasternal long axis cut showing the left ventricle (LV), left atrium (LA), and where the measurements *a*, *b*, *c*, *d*, and *g* were made on the still frame photographs. *g* is the diameter of the pulmonary trunk at the level of the pulmonary valve; *d* is the smallest distance in systole between the anterior mitral leaflet and the interventricular septum; the line *a*+*b* joins the anterior point of insertion of the pulmonary valve and the most apical point of the endocardial surface of the left ventricular cavity; *c* is a perpendicular line from the point of maximum septal bulge back to the line *a*+*b* that determines the distances *a* and *b*.

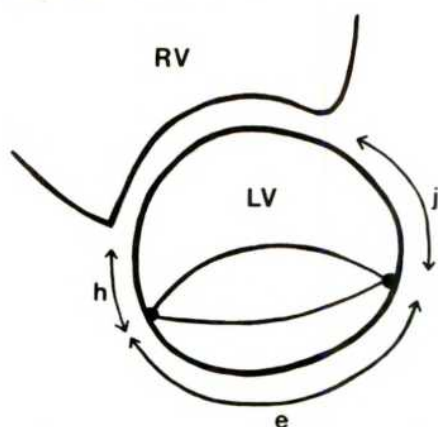


Fig. 2 Diagrammatic representation of parasternal short axis at the level of the tips of the mitral valve cut showing the left ventricle (LV), right ventricle (RV) and where the measurements *e*, *j*, and *h* were made from the still frame photographs. *e* is the distance between the endocardial attachments of the anterolateral and posteromedial papillary muscles. *h* and *j* are the distances of the papillary muscles from the interventricular septum and *f* (see text) is the endocardial LV circumference.

diameter of the pulmonary valve annulus (*g*) at the same time (Fig. 1). The ratios *h*:*f*, *j*:*f*, and (*h*+*j*):*f* were measures of the closeness of the papillary muscles to the interventricular septum (*f* is the endocardial circumference of the left ventricle) and *e*:*f* a measure of the closeness of the papillary muscles to each other (Fig. 2). We excluded from further analysis those patients who underwent surgery between cardiac catheterisation and echocardiography, those in whom the interval between cardiac catheterisation and cross sectional echocardiographic study was greater than three days, and those who had post-

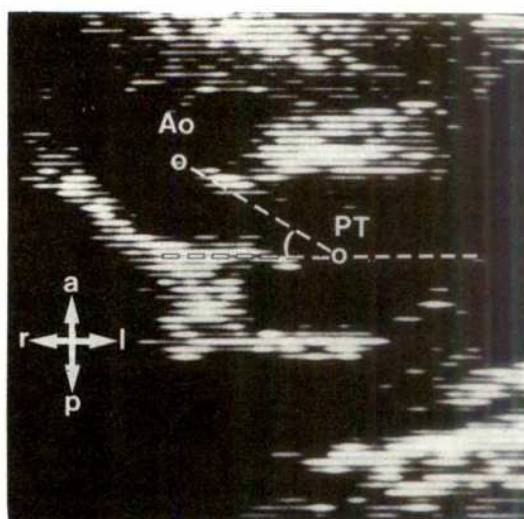


Fig. 3 Parasternal short axis cut at the level of the great vessels showing the method of measurement of the angle between them. A horizontal line was drawn through the midpoint of the pulmonary trunk (PT) and a further line was drawn to join this to the midpoint of the aorta (Ao). The angle between these lines was the great vessel angle. *a*, anterior; *l*, left; *p*, posterior; *r*, right.

operative studies only. Forty patients formed the remaining study group (26 male and 14 female, aged 0-497 days mean 79.6). Twenty two patients were aged <3 days and all of them had cross sectional echocardiography on the same day as the haemodynamic study. We analysed the haemodynamic and cross sectional echocardiographic measurements by Student's *t* test and by multiple regression analysis using the Statistical Package for the Social Sciences (version 7.0 Northwestern University) on an Amdahl mainframe computer.

Results

Pronounced septal bulge was common in patients with no pressure gradient between left ventricle and pulmonary artery. Thus septal bulge on its own did not necessarily indicate either fixed or dynamic obstruction. Seven patients had fixed abnormalities of the left ventricular outflow tract recognised by cross sectional echocardiography. In two this was a subpulmonary membrane (Fig. 4) analogous to a subaortic membrane seen in patients with normally related great vessels. In one this was confirmed at operation. In another the tension apparatus of the mitral valve appeared to be inserted into the ventricular septum (Fig. 5) and this was much more obvious in real time scanning than on still frames.

In the remaining four cases there was pronounced

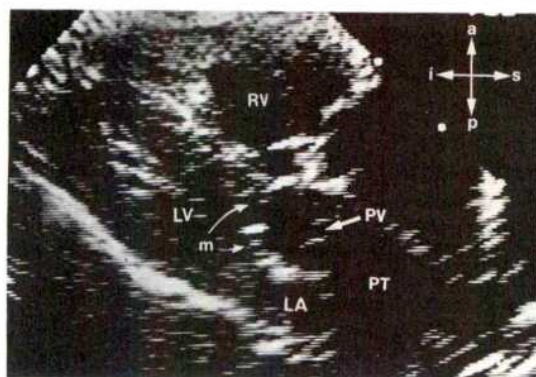


Fig. 4 Apical long axis cross sectional echocardiographic cut showing a subpulmonary membrane (m) attached to both the interventricular septum and anterior mitral leaflet below the pulmonary valve (PV). a, anterior; i, inferior; LV, left ventricle; LA, left atrium; p, posterior; PT, bifurcating, posteriorly situated pulmonary trunk; RV, right ventricle; s, superior.

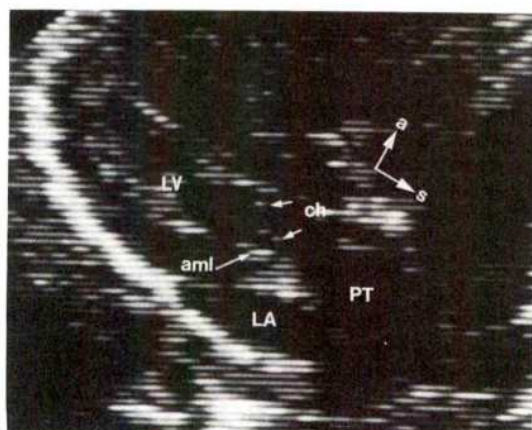


Fig. 5 Parasternal long axis cross sectional echocardiographic cut showing abnormal chordal attachment (ch) from the anterior mitral leaflet (aml) to the interventricular septum across the left ventricular outflow tract. a, anterior; LA, left atrium; LV, left ventricle; PT, pulmonary trunk; s, superior.

thickening and ridge formation either about halfway along the anterior mitral leaflet or on the left side of the interventricular septum directly opposite this point, or else at both points (Fig. 6a and b). Real time scanning in these four patients showed that there was a characteristic motion of the septum and anterior and posterior mitral leaflets, such that in systole the relatively immobile anterior leaflet was firmly clamped between septum and posterior leaflet, thus producing left ventricular outflow obstruction. This pattern was quite distinct from that found in patients with septal

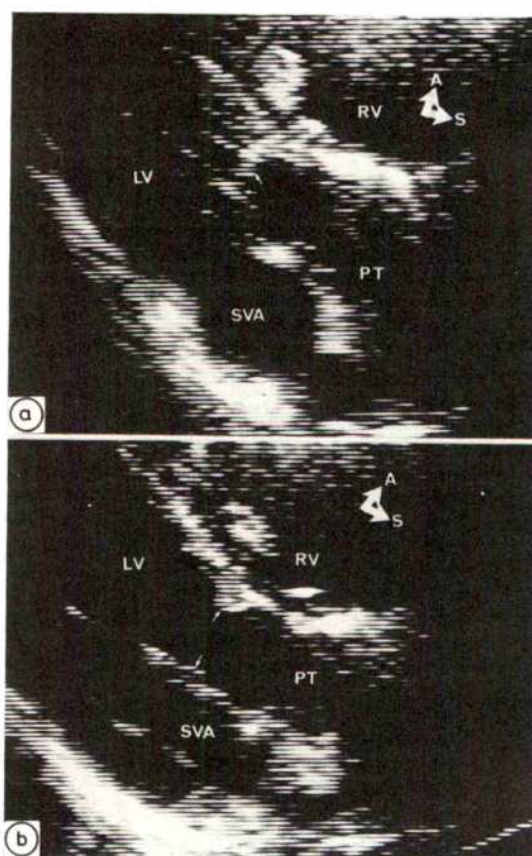


Fig. 6 Parasternal long axis cuts from a patient with fibrous thickening (arrows) on the interventricular septal endocardial surface at the point of mitral septal apposition and on the anterior mitral leaflet. a, anterior; LA, left atrium; LV, left ventricle; p, posterior; PT, pulmonary trunk; RV, right ventricle; s, superior; SVA, systemic venous atrium.

bulge alone; although the septum bulged posteriorly in these patients, the anterior mitral leaflet was not squeezed. In two of the four patients with this form of septal and mitral obstruction, successive cross sectional echocardiograms showed progressive anatomical obstruction but cardiac catheterisation was not repeated. Systolic pressure gradients were known in five of the seven patients with fixed obstruction (20, 30, 56, 63, and 100 mm Hg). The gradient of 20 mm Hg occurred in a patient with a membrane a few millimetres below the pulmonary valve and the 30 mm gradient in another patient who had excessive thickening of the anterior mitral leaflet and the interventricular septum at their point of apposition. The four patients with septal/mitral apposition were analysed separately, but no significant correlations were found between systolic gradients and geometric variables,

apart from that expected with d:g.

The only statistically significant ($p < 0.001$) difference in mean values of left ventricular geometric ratios and haemodynamic variables between the groups with and without fixed obstruction was that for d:g ratios (fixed obstruction $n=7$, $d:g=0.002$, no (fixed obstruction $n=40$, $d:g=0.1870$).

Patients who had no cross sectional echocardiographic evidence of anything other than uncomplicated septal bulge were included in the "no fixed obstruction" group for analysis. They had systolic gradients ranging from 0 to 40 mm Hg (mean (SD) 15.1 (2.7)). The highest gradients found were 21, 35, 38, and 40 mm Hg. None of these patients had angiographic, surgical, or necropsy (one patient) evidence of fixed obstruction.

LONG AXIS MEASUREMENTS

The ratio $c:(a+b)$ was directly related to right ventricular peak systolic pressure ($r=0.277$, $p=0.042$, $n=40$) and $c:g$ was directly related to right ventricular pressure ($r=0.350$, $p=0.013$, $n=40$) (Fig. 7), and possibly to the amount by which right ventricular systolic pressure exceeded left ventricular systolic pressure ($r=0.261$, $p=0.052$, $n=40$). No measure of septal bulge or septal eccentricity correlated with the systolic gradient from left ventricle to pulmonary artery. The ratio d:g was inversely, albeit weakly, related to systolic gradient ($r=0.403$, $p=0.048$, $n=18$) (Fig. 8) and to the amount by which right ventricular systolic pressure exceeded left ventricular systolic pressure ($r=0.295$, $p=0.032$, $n=40$). This ratio d:g was directly related to left ventricular systolic pressure ($r=0.271$, $p=0.046$, $n=40$) and pulmonary arteriolar resistance index ($r=0.692$, $p=0.006$, $n=12$). Among the patients in whom fixed obstruction was excluded

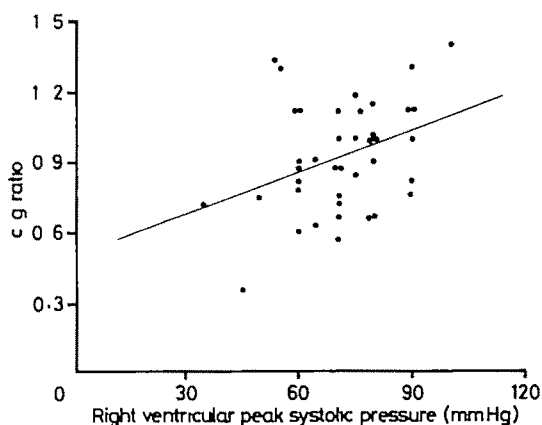


Fig. 7 Correlation of the ratio $c:g$ (a measure of degree of septal bulge) and peak right ventricular systolic pressure ($n=40$, $r=0.350$, $p=0.013$).

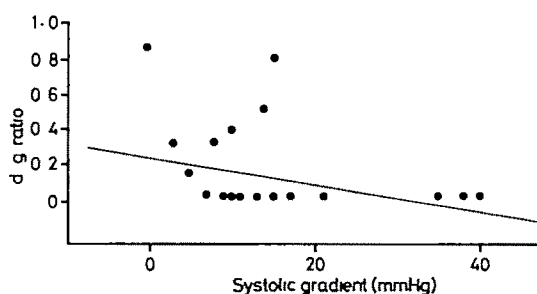


Fig. 8 Correlation between the ratio d:g (a measure of the minimum systolic distance between the anterior mitral leaflet and the interventricular septum) and peak systolic gradient across the left ventricular outflow tract ($n=18$, $r=-0.403$, $p=0.048$).

echocardiographically, only those whose gradient from left ventricle to pulmonary artery was < 20 mm Hg did not have complete mitral/septal apposition ($d:g=0$) at end systole (Fig. 9). When d:g was zero, however, there were similar numbers of patients with gradients greater than and less than 20 mm Hg, indicating that systolic apposition of the anterior mitral leaflet to the septum is not necessarily associated with obstruction.

SHORT AXIS MEASUREMENTS

Neither closeness of the papillary muscles to each other (e:f), nor closeness of the individual papillary muscles (h:f, j:f) to the interventricular septum were

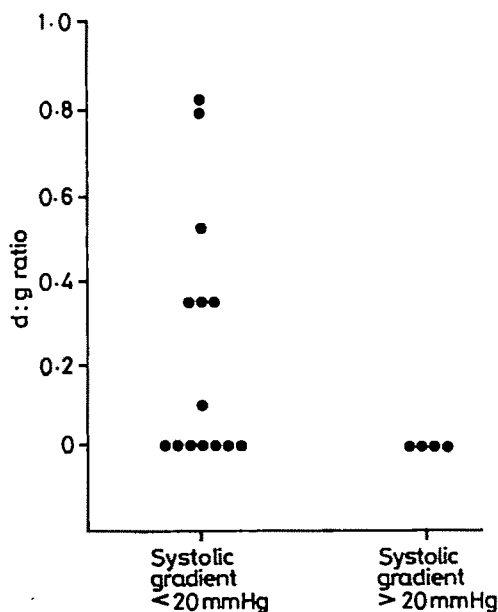


Fig. 9 Comparison of d:g ratios in patients with peak systolic gradients of > 20 mm Hg and < 20 mm Hg across the left ventricular outflow tract.

significantly related to any haemodynamic variable. There was no significant correlation between any long axis measurement and the short axis measurements, but $d:g$ was related to septal bulge ($c:(a+b)$) ($r=-0.516$, $p=0.001$, $n=40$).

SHORT AXIS MEASUREMENT OF GREAT VESSEL ANGLE

The angle between the aorta and pulmonary trunk was not significantly related to systolic gradient or to the ratio of ventricular systolic pressures but it was positively related to $h:f$ ($r=0.597$, $p=0.045$, $n=9$) and $(h+j):f$ ($r=0.852$, $p<0.002$, $n=9$) (Fig. 10).

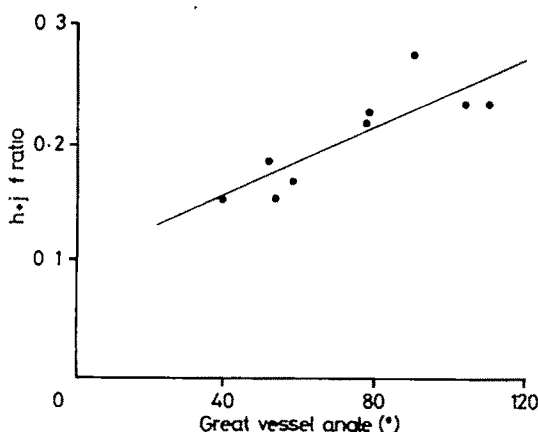


Fig. 10 Correlation of the ratio of the sum of the distances of the mitral papillary muscles from the interventricular septum $h+j$ (see Fig. 6) to the endocardial circumference (f) of the left ventricle with great vessel angle (see Fig. 6) ($n=9$, $r=0.852$, $p<0.002$).

Discussion

Despite many published reports, little is understood about the origin of left ventricular outflow tract obstruction in simple transposition of the great vessels when the ventricular septum is intact. Postmortem studies give no information on the haemodynamic consequences of septal bulge. The information that we have is derived from haemodynamic studies, angiocardiology, and M mode and pulsed Doppler echocardiography. In simple transposition there is usually some gradient between the left ventricular peak systolic pressure and the pulmonary artery pressure.⁷

In an angiocardiology study, Silove and Taylor implicated anterior movement of the mitral valve in systole as the cause of left ventricular outflow tract obstruction. They drew attention to the similarities between the appearance of the line of contact between

the mitral valve and septum in simple complete transposition and that in hypertrophic obstructive cardiomyopathy.⁷ They reached this conclusion, however, after selecting 17 patients with intact ventricular septum and an anatomical abnormality which was visible on frontal and lateral plane angiocardiology from among 41 patients with peak systolic gradients of ≥ 15 mm Hg between left ventricle and pulmonary artery. They were not able to explain the presence of this gradient in 16 of the remaining 24 patients in whom no angiocardiology abnormality was present in the left ventricular outflow tract. Sansa and colleagues used axial cineangiographic techniques to determine the angiocardiology features of left ventricular outflow tract obstruction in transposition.¹⁵ Their study confirmed the presence of most of the anatomical abnormalities associated with left ventricular outflow tract obstruction, including septal bulge, but pressure measurements made at cardiac catheterisation were not given.

Most investigations by M mode and pulsed Doppler echocardiography have not distinguished between patients with and those without ventricular septal defect. This makes interpretation of most of the results difficult, since it would be surprising if patients with complete transposition and ventricular septal defect, in whom a fibromuscular subpulmonary tunnel is common, did not have abnormalities in M mode and pulsed Doppler echocardiographic recordings. Nanda and colleagues reported that transposition with left ventricular outflow tract obstruction was characterised by diastolic mitral/septal apposition, a pulmonary artery small in comparison with the aorta, localised subpulmonary narrowing on scanning from left ventricle to pulmonary artery and, in a few patients, anterior motion of the mitral valve in systole, asymmetric septal hypertrophy, and systolic closure of the pulmonary valve.¹⁶ Few of these criteria have become established. Aziz and colleagues distinguished between two types of obstruction, "fixed" in which the diameter of the left ventricular outflow tract compared with the diameter of the pulmonary artery was reduced throughout the cardiac cycle and in which there was no systolic anterior motion of the mitral valve, and "dynamic", in which the left ventricular outflow tract was wide open during diastole but narrowed in systole.¹⁷ All these patients with dynamic obstruction had anterior motion of the mitral valve in systole. Seven out of eight patients with "fixed" obstruction had an associated ventricular septal defect and, of those patients with so called dynamic obstruction, two had a ventricular septal defect. Fifteen out of the total of 16 patients had already undergone repair of transposition by Mustard's operation. Furthermore, the mean systolic pressure gradient between left ventricle and pulmo-

nary artery in the patients with dynamic obstruction was only modest (23.2 (12.9) mm Hg). There was no difference in the ratio between the left ventricular outflow tract diameter and the pulmonary artery diameter in patients with dynamic obstruction and patients with no obstruction at all. These workers subsequently reported further findings in a much larger series of patients,¹⁸ including 36 with left ventricular outflow tract obstruction, but their results are again difficult to interpret because they do not distinguish between patients with and those without ventricular septal defect. Silverman and colleagues showed that systolic anterior motion of the mitral valve occurred in six out of 10 patients after Mustard's operation for simple transposition; all six had a peak systolic left ventricular/pulmonary artery gradient of ≤ 25 mm Hg.¹⁹

Johnson *et al*, evaluated 21 consecutive children with simple transposition before interatrial repair and found no correlation between the presence of a haemodynamic pressure gradient from the left ventricle to the pulmonary artery and any of the features previously regarded as diagnostic of left ventricular outflow tract obstruction, including systolic anterior motion of the mitral valve, pulmonary valve flutter, and premature closure of pulmonary valve during systole.²⁰ Pulsed Doppler velocimetry detected left ventricular outflow tract obstruction in complete transposition of the great arteries²¹ but gave no indication of the severity of obstruction. The number of patients with an intact ventricular septum was not stated.

Although septal bulge is prevalent in simple transposition after the first few days of life²² and has been implicated in left ventricular outflow tract obstruction^{5,6} little work has been done to confirm its role in the development of this obstruction. Our results suggest that septal bulge is usually associated with, and presumably the result of, the high right ventricular pressure and low pulmonary vascular resistance that typify patients with simple transposition. The greater the difference between the right and left ventricular systolic pressures, and the lower the pulmonary vascular resistance, the more the left ventricle is squashed by the right ventricle. These cross sectional echocardiographic findings in patients with complete transposition accord with those reported, with a single exception, in patients without transposition.^{23,24}

We found no correlation between the degree of septal bulge and peak systolic gradient across the left ventricular outflow tract and only a very weak correlation between that gradient and the degree of proximity of the anterior mitral valve leaflet to the septum. These findings are surprising in view of the fact that Yacoub and colleagues found that left ventricular outflow tract gradients disappeared in patients studied

before and after anatomical correction of simple transposition.⁵ Reversing the pressures in the two ventricles would presumably reduce septal bulge and therefore the left ventricular outflow gradient if this were the cause of the gradient. Other factors, such as reduction in flow, may account for the disappearance of the outflow gradient after anatomical correction.

Two aspects of mitral/septal apposition merit further discussion. Firstly, it is by no means always the result of systolic anterior motion of the mitral valve. In many patients parasternal long axis views show that such apposition is due to posterior septal motion rather than to anterior mitral displacement. Secondly, there may be complete apposition of the two structures in the absence of any gradient. The retrospective nature of this study does not allow us to explain this finding. In a prospective study where pressures, cross sectional echocardiograms, and electrocardiograms were measured simultaneously, it could be established whether complete apposition coincided with a lack of a gradient, and, if it did, the importance of timing of such apposition could be examined. If it were to occur sufficiently late in systole it might not produce obstruction, as has been suggested by Murgo and colleagues in hypertrophic cardiomyopathy.²⁵ Whatever the reason for the lack of association between mitral/septal apposition and left ventricular outflow tract obstruction, it seems clear that the term "dynamic left ventricular outflow tract obstruction" should either be clarified or abandoned. Such a condition certainly cannot be diagnosed on the basis of the echocardiogram or angiocardiogram alone.

Unlike Chiu and colleagues,¹³ we could find no correlation between the angle of the great vessels and the systolic gradient across the left ventricular outflow tract, but we did find that great vessel angle was significantly and positively related to $h:f$ and $(h+j):f$. The more the great arteries run side by side the less wedged was the pulmonary valve and the nearer were the papillary muscles to the septum.

Our findings confirm that cross sectional echocardiography can identify some fixed abnormalities of the left ventricular outflow tract in cases of simple transposition. We cannot exclude the possibility that fixed obstruction was present but missed; but since fixed obstruction is rare in anatomical specimens it is unlikely that many errors were made. We have also shown that when the left ventricular outflow tract appears to be normal the gradient across it will be < 20 mm Hg. We have used cross sectional echocardiography to demonstrate that thickening of the interventricular septum and anterior mitral leaflet at their point of coaptation can cause progressive anatomical left ventricular outflow tract obstruction in some patients, as Tynan and colleagues have suggested might occur.⁶

This confirms what has long been suspected from pathological studies—that the fibrous plaque seen on both septum and anterior mitral leaflet is acquired rather than congenital.

PJR was supported by the Wellcome Trust, and FJM and RKH by the Vandervell and British Heart Foundations.

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Non-invasive assessment of pulmonary blood supply after staged repair of pulmonary atresia

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SUMMARY Radionuclide studies were performed to determine pulmonary blood flow in six children who had undergone surgery for pulmonary atresia, ventricular septal defect, and hypoplastic pulmonary arteries with or without major aortopulmonary collateral arteries. Lung blood flow was assessed from both particle perfusion lung scans and the pulmonary and systemic phase of a radionuclide dynamic flow study. Five patients had perfusion defects identified on the particle perfusion lung scan. In three of these, abnormal areas were perfused only during the systemic phase of the flow study, a combination of findings that indicate the presence of perfusion by collateral arteries. In one patient no systemic perfusion was noted and in one an initial particle perfusion study indicated the presence of a lung segment perfused by a collateral artery. In this last patient the particle perfusion scan after total correction showed a reduction in the size of the lung perfusion defect and no evidence of lung perfusion during the systemic phase of the flow study. The particle perfusion lung scan in the sixth patient showed pronounced asymmetry in blood flow to the lungs with no segmental perfusion defect on the particle perfusion scan and no abnormalities on the systemic flow study.

It is concluded that radionuclide lung perfusion and flow studies provide useful information on lung perfusion and merit further evaluation to define their role in the management of these patients.

There is still debate regarding the surgical management of patients with pulmonary atresia, ventricular septal defect, and hypoplastic pulmonary arteries with or without major aortopulmonary collateral arteries.¹ It is, however, generally agreed that the long term results of surgery depend on achieving maximal direct segmental perfusion of the lungs and satisfactory relief of right ventricular outflow tract obstruction.²⁻⁴

After each staged palliative operation haemodynamic and angiographic investigations are usually performed. The numbers of invasive investigations should be reduced if possible as each adds morbidity and discomfort for the patient. Non-invasive radionuclide assessment of lung blood flow has the potential for this.

We report our experience with radionuclide studies

in determining pulmonary blood flow in six patients with this complex abnormality. Six underwent studies postoperatively and one was also investigated preoperatively.

Patients and method

Six patients were studied (age range 6-15 years). Each had pulmonary atresia, ventricular septal defect, and hypoplastic pulmonary arteries, five with and one without collateral arteries. Table 1 shows the past history and clinical data of each patient at the time of radionuclide investigation.

RADIONUCLIDE DATA ACQUISITION

After informed consent was obtained an intravenous cannula was inserted into a brachial vein. A two stage scintigraphic procedure was then performed. Firstly, a standard multiple view lung particle perfusion scan was performed using a small field of view gamma-camera fitted with a general all purpose low energy

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Accepted for publication 22 March 1985

Table 1 *Patient data*

Case No	Major aortopulmonary collateral arteries (MAPCA)		Other procedures before repair	Catheterisation findings after repair
	Site	Management		
1	Bilateral collaterals	{ Left lung, ligated Right upper/middle lobes, no intervention	Right ventricular outflow tract reconstruction	
2	Bilateral collaterals	{ Right upper/middle lobes,* transplanted Left lower lobe,* no intervention	Right ventricular outflow tract reconstruction, right pulmonary arterioplasty	Residual MAPCA left lower lobe
3†	Major collateral with bilateral supply	Ligated	Right ventricular outflow tract reconstruction, right pulmonary arterioplasty	Large left to right shunt, no significant residual collaterals noted
4	Bilateral collaterals	Communicating left pulmonary artery, ligated Left lower lobe, ligated Left lower lobe, transplanted Right upper/middle lobes, transplanted Right middle/lower lobes, ligated Right lower lobe, transplanted	Ascending aorta to right pulmonary artery shunt	
5	Bilateral collaterals	Left superior, transplanted Left inferior, ligated	Main pulmonary artery to ascending aorta anastomosis, right pulmonary arterioplasty	
6	None		Waterston shunt	Right pulmonary artery 18 mm, left pulmonary artery 7 mm

*Sole blood supply.

†No blood supply seen to right middle lobe preoperatively

collimator. A dose of technetium-99m labelled macroaggregated albumin was calculated by patient weight based on an adult dose of 1 mCi (37 MBq). With the patient lying supine, scintigraphic data were acquired on transparencies and a dedicated minicomputer (DEC 11/34 computer using Gamma-11 software). The scans initially acquired were in the anterior and left and right lateral views. If there was evidence of a right to left cardiac shunt extra scans were recorded of the head and the kidneys. This phase of the study finished with a posterior lung scan with the patient lying supine above the gammacamera.

Secondly, a dynamic radionuclide flow study was

acquired immediately after the last lung particle perfusion scan and without the patient moving in relation to the gammacamera. For this study technetium-99m as pertechnetate was injected as a bolus and images were acquired on to transparencies as sequential two second views and also into the computer as a one frame per second dynamic study for 50 seconds after bolus injection. The dose of technetium-99m used was calculated according to patient weight and based on an adult dose of 20 mCi (740 MBq).⁵

DATA ANALYSIS

A recent chest radiograph was available for each patient to help in the interpretation of the scans. The

Table 2 *Radionuclide study data*

Case No	Defect on lung particle perfusion scan	Dynamic lung flow scan	
		Pulmonary phase defect	Systemic phase visualisation
1	Right upper lobe	Right upper lobe	Right upper lobe
2	Left lower lobe	Left lower lobe	Left lower lobe
3*	Right middle lobe	Right middle lobe	Right middle lobe
4	Bilateral defects	Normal	Normal
5	†Left upper lobe	—	—
5	‡Smaller defect	Normal	Normal
6	Right lung: left lung flow ratio 6.7:1	Increased flow to right lung	Normal

*No blood supply seen to right middle lobe preoperatively.

†Lung particle perfusion study only performed after transplant of major aortopulmonary collateral artery to right lower lobe.

‡Combined study performed after transplant of major aortopulmonary collateral artery to left upper lobe and total repair.

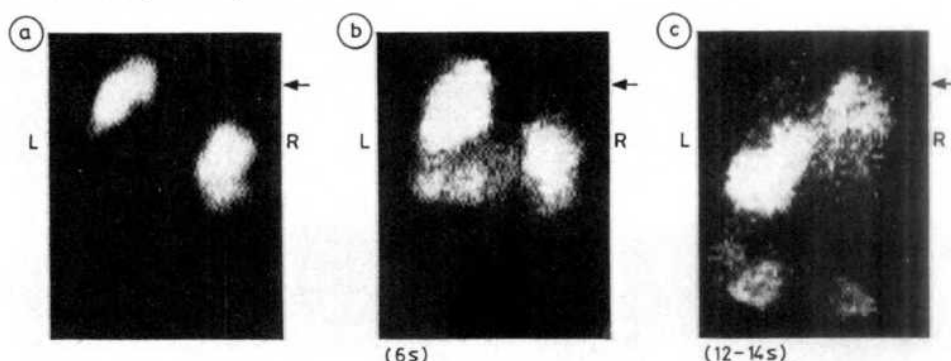


Fig. 1 Case 1: (a) particle perfusion lung scan in posterior view showing the right upper lobe perfusion defect (arrow). The perfusion defect (arrow) is also shown in (b) the lung phase of the technetium-99 flow study, with perfusion in (c) the systemic phase of that study. L, left; R, right.

relative perfusion of each lung from the pulmonary arteries was calculated from the digital images of the particle perfusion scan as a ratio of the arithmetic mean activity of the anterior and posterior images of each lung. The particle perfusion scans were then visually examined for the presence of segmental defects representing areas of the lung that were not perfused from the pulmonary arteries.

To assess whether the defects corresponded to areas perfused by collateral arteries the first pass radionuclide flow study was reformatted as sequential one second images and then examined in a closed loop cine format in conjunction with the sequential transparencies. Perfusion of lung segments by functioning collateral arteries was inferred if the underperfused areas on the particle perfusion lung scan filled in on the radionuclide flow study only after the bolus of tracer had passed through the left ventricle and out of the aortic outflow tract in the systemic phase of the scintigraphic flow study.

Results

Table 2 summarises the results of the lung perfusion studies and ventricular function.

SCINTIGRAPHIC FINDINGS

Of the six patients, five had perfusion defects identified on the particle perfusion lung scan. In three of these, abnormal areas were perfused only during the systemic phase of the radionuclide flow study, whereas in one no systemic perfusion was noted. In the fifth patient initial scintigraphic abnormalities were reduced in a subsequent study performed after total correction. The radionuclide studies in the sixth patient showed pronounced asymmetry in blood flow to the lungs with no segmental perfusion defects on the particle perfusion scan and no abnormalities on the systemic phase of the flow study.

Case 1—This patient, who underwent repair early in our series, had had two collateral arteries, one to each lung. The right sided collateral supplied the right upper and middle lobes. No collateral artery transplant was performed, but the left sided collateral artery was ligated. At scintigraphic assessment post-

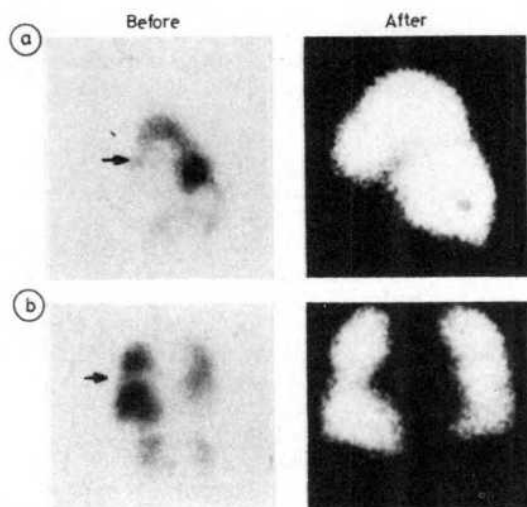


Fig. 2 Case 5: particle perfusion lung scans in (a) the left lateral and (b) posterior views before and after operation showing absent perfusion to all but the apical segment (arrow) of the left upper lobe preoperatively. The perfusion defect over the right lung was explained by a pleural effusion present on a chest radiograph. Note bilateral kidney visualisation on the preoperative posterior image (b) indicating significant right to left shunting. Postoperatively the left upper lobe perfusion defect is much smaller and there is no evidence of right to left shunting.

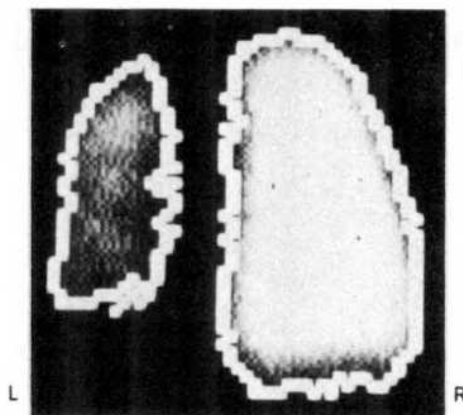


Fig. 3 Case 6: digital image in the posterior view of a postoperative particle perfusion lung scan showing relative pulmonary perfusion to right and left lungs estimated from the ratio of counts obtained within each lung field (left 48 000, right 320 000; right to left ratio 6.7:1). L, left; R, right.

operatively this patient had a perfusion defect in the right upper lobe, as seen on the posterior image of the particle perfusion scan (Fig. 1). This defect was confirmed on the pulmonary phase of the flow study (Fig. 1). Perfusion of this segment was clearly identified on the systemic phase of the flow study (Fig. 1). This finding was considered to confirm perfusion of the lung segments by the known persisting collateral artery.

Case 2—Angiographic confirmation of a collateral artery was obtained in a further patient (case 2), in whom a combination of scintigraphic findings similar to those in case 1 was observed in the left lower lobe, suggesting a blood supply of this region by a collateral artery.

Case 3—This patient had underperfused areas on the particle perfusion lung scan and on the lung phase of the flow study with systemic flow to the right middle lobe. Previous invasive studies had failed to show any blood supply to this region. This was thought to suggest an angiographically unrecognised collateral artery.

Case 4—This patient had multiple areas of underperfusion on both the particle perfusion lung scan and the pulmonary phase of the flow study. These areas did not appear to be due to perfusion by collateral arteries since they were not seen to perfuse on the systemic phase of the flow study.

Case 5—This patient had a particle perfusion lung scan before and both a particle perfusion and flow study after his final repair. At initial contrast angiography collateral arteries were identified as the sole blood supply to the right lower lobe and to most of the left upper lobe. At his first operation the collateral

artery supplying the right lower lobe was successfully transplanted to the native pulmonary artery. The first scintigraphic study was performed after this surgical procedure. The expected right to left shunt was reflected on the particle perfusion scan by visualisation of the kidneys (Fig. 2). Particle perfusion lung scans showed preserved perfusion to the apical segment of the left upper lobe with underperfusion of the remainder of that lobe. He then underwent transplantation of the second collateral artery to the left upper lobe and subsequent total repair. Postoperatively, a repeat scan showed that the features of the right to left shunt had been abolished and the size of the perfusion defect in the left lung was reduced (Fig. 2). The flow study did not show any lung flow during the systemic phase to suggest residual lung perfusion by collateral arteries.

Case 6—This patient had no collateral arteries. A Waterston shunt had been performed at 3 months of age. One year after total repair a follow up cardiac catheterisation showed a pronounced difference in the size of the right and left pulmonary arteries. The lung scan showed pronounced asymmetry of blood flow to the lungs (Fig. 3) with a right to left lung perfusion ratio of 6.7 to 1.0. The ratio of the calculated areas of the two pulmonary arteries from the cardiac catheterisation data (Table 1) was very similar to the radionuclide perfusion ratio. There were no focal perfusion defects in either lung field. There were no abnormalities on the systemic phase of the flow study, although its pulmonary phase also showed the increased blood flow to the right lung.

Discussion

The possibility of distinguishing pulmonary arterial flow from "bronchial" collateral flow using sequential intravenous and intra-aortic injection of indium-131 labelled macroaggregated albumin was initially described by Friedman *et al* in patients with congenital heart disease.⁶ More recently, Baker *et al* used selective injections of radionuclide labelled albumin microspheres for this purpose in patients with pulmonary atresia during cardiac catheterisation.⁷ Studies to evaluate the systemic origin of the vascular supply in cases of bronchopulmonary by sequestration radionuclide angiography using technetium-99m as pertechnetate have been reported in five children.⁸ Particle perfusion studies have been used with intravenous injections to evaluate pulmonary blood flow in patients with tetralogy of Fallot before⁹ and after total repair.^{9,10} This technique alone, however, is limited in that it provides no information on lung blood flow arising from systemic collaterals. There have been two previous reports, each describing one case, in which the combination of particle perfusion lung scans and

radionuclide flow studies has been used to assess pulmonary blood flow more comprehensively, using intravenous injections of tracers.^{11 12}

To our knowledge this is the first description of the use of lung particle perfusion combined with radionuclide flow studies to assess both pulmonary and systemic blood flow to the lungs in patients with pulmonary atresia, ventricular septal defect, and hypoplastic pulmonary arteries with or without collateral arteries.

The surgical management of this complex abnormality requires a precise understanding not only of the intracardiac anatomy but also of the pulmonary blood supply.¹³⁻¹⁵ Initial cardiac catheterisation is performed to obtain necessary information on the intracardiac defect, the presence or absence of central pulmonary arteries and whether they are confluent or not, their connections with the intrapulmonary arteries, the number, origin, connections, and distributions of collateral arteries, and the presence of stenosis of the pulmonary arteries or of collateral arteries.

Follow up catheterisation is usually performed before each stage of surgical repair to identify residual abnormality. Uneven growth with residual stenoses of central pulmonary arteries has also been described by Kirklin in his review of Freedom *et al.*¹ Right ventricular outflow tract patches, peripheral shunts, and collateral artery transplantation all have the potential of producing stenosis.^{16 17} There may be persistence of stenosis or occlusion of transplanted collateral arteries or residual arborisation defects due to previously unrecognised collateral arteries.

Angiographic demonstration of the central pulmonary arteries and of collateral arteries may not be fully satisfactory.^{3 4} Other techniques include computed axial tomography¹⁸ and radionuclide perfusion and dynamic flow scintigraphy. The latter appears to be a less traumatic alternative with greater sensitivity for abnormal lung blood flow. Pulmonary particle perfusion scans undoubtedly provide precise and reliable information regarding pulmonary blood flow abnormalities. The technetium-99m labelled particulate material injected is filtered out at the first downstream capillary bed encountered. Areas of decreased pulmonary arterial perfusion appear as areas of decreased radioactivity. Adequate evaluation of scintigraphic data requires correlation with a recent chest radiograph. For example, one of our patients (case 5) showed a large perfusion defect over the right lung, which was explained by a pleural effusion (Fig. 2). Right to left shunts can be detected because particles bypass the lung capillary system and radioactivity appears in the systemic circulation in brain and kidneys.

The dynamic flow study assesses both pulmonary

blood flow and systemic arterial flow to the lungs. Early entry of radioactive material to the aorta as a result of right to left shunting may complicate separation of the two phases. In the absence of significant right to left shunting areas of lung perfused by collateral arteries are visualised only during the systemic arterial phase.

We have identified various combinations of patterns on lung particle perfusion scintigraphy and flow study. Firstly, areas of underperfusion seen on the particle perfusion study and pulmonary phase of the flow study, and perfused only during the systemic phase of the flow study (Fig. 1), strongly suggest the presence of lung perfusion by residual collateral arteries. This suspicion was confirmed in one of our patients at postoperative cardiac catheterisation. One other patient with a similar combination of data was known to have a collateral artery which had not been dealt with at surgery.

Secondly, areas of underperfusion seen on both the particle perfusion lung scan and the pulmonary phase of the flow study, and in which no matching perfusion is seen during the systemic phase of the flow study, indicate lung segments without appreciable blood supply of either pulmonary or systemic origin. These may be due either to ligation or occlusion of collateral arteries representing the sole supply of lung segments or to areas of lung tissue abnormality. Impaired growth of the alveoli with a reduction in their number may be caused by prolonged hypoxia and diminished blood flow.¹⁵ The small residual postoperative perfusion defect in the patient in case 5 (Fig. 2) may be of this type.

Thirdly, homogeneous pulmonary perfusion on particle perfusion scans associated with a normal systemic phase on the flow study was seen only in patients without residual functioning collateral arteries, even in the presence of asymmetrical flow due to pronounced difference in growth between the two pulmonary arteries. Digitisation of the particle perfusion scan enables relative flow to individual segments in the same lung or to each lung field to be assessed quantitatively,¹⁰ as in the patient in case 6, in whom the pronounced asymmetry in blood flow to the lungs was due to the difference in growth between the two native pulmonary arteries. After a Waterston shunt, patterns showing either increased,⁹ as in the patient in case 6 (Fig. 3), or decreased¹⁰ lung particle perfusion in the lung that had received the shunt have been previously described.

Fourthly, an additional possibility, not seen in our patients, should be considered. Unrecognised or untreated collateral arteries, connected to the native pulmonary arteries, can be suspected if areas of lungs already perfused during the perfusion study appear again during the systemic phase of the flow study.

The management of the patient with pulmonary atresia, ventricular septal defect, and hypoplastic pulmonary arteries remains a problem, in particular when collateral arteries with or without arborisation defects are present. Uniform growth of the pulmonary artery system, and unifocalisation of blood supply when collateral arteries are present, are desirable as a prelude to corrective surgery, but abnormal lung perfusion may persist even after total repair.

Repeated evaluations are necessary, and angiography is currently usually performed to assess the results of the staged surgical procedures, often after each operation. Contrast angiography can precisely define the size and growth of pulmonary arteries and is essential both in the initial preoperative evaluation and immediately before and after final repair. To repeat this investigation after every staged palliative procedure before final repair would, however, not be entirely necessary when a precise anatomical assessment of pulmonary blood vessels is not needed, if a simpler relatively non-invasive technique was readily available to assess the physiological effects of each staged procedure. Our limited comparison of the results of postoperative cardiac catheterisation with combined radionuclide blood flow studies suggests that these radionuclide techniques have some potential to identify areas of lung perfused by functioning collateral arteries and residual right to left shunts and therefore may be of value as a non-invasive follow up investigation in this clinical situation.

These scintigraphic studies may also be potentially useful in the preoperative period to direct selective angiography or to clarify further lung perfusion patterns, reducing the need for prolonged exposure to radiation from multiple contrast angiograms. A specific factor which may particularly limit the diagnostic value of this non-invasive technique before surgical intervention is the presence of major shunting from right to left (as in the initial study in the patient in case 5) or, to a lesser extent, from left to right. The pulmonary and systemic phases are not discrete under these circumstances, and inaccuracies in the quantitative prediction of the contribution of regional blood flow of the various sources would be inevitable. Because of these considerations, radionuclide methods may be of most value in the preoperative assessment of these patients when selective injection of radiolabelled particles is performed at the time of the definitive cardiac catheterisation.⁷

It is likely that a specific limitation of radionuclide techniques could be, for example, the difficulty in identifying perfusion by collateral arteries to the left lower lobe because of overlap with the left ventricle. Nevertheless, our data indicate that radionuclide techniques merit further evaluation to assess their possible role in the overall management of these

patients, especially when collateral arteries are present.

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Case reports

Spontaneous recanalisation of side branches occluded during percutaneous transluminal coronary angioplasty

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SUMMARY Percutaneous transluminal coronary angioplasty was performed in a 56 year old man with postinfarction angina. During an otherwise uncomplicated dilatation of a left anterior descending artery with a 70% stenosis two diagonal branches, each measuring 1.5 mm in diameter, were occluded. The occlusions were not associated with any adverse clinical effects, though there was a small rise in plasma creatine kinase concentration. The patient became free of angina two weeks after angioplasty, and follow up angiography showed spontaneous reappearance of the occluded side branches. Redistribution of atheromatous material and its later reabsorption may have been the mechanism for the initial occlusion and later reappearance of the vessels.

Side branch occlusion is a recognised complication of percutaneous transluminal coronary angioplasty. Side branches originating directly in the stenotic segment have been shown to be particularly at risk, and it is often a contraindication to coronary angioplasty.¹ In the absence of a systematic follow up study of these occluded side branches, the assumption is that these vessels would remain permanently blocked. We report the spontaneous recanalisation of two diagonal branches occluded during an otherwise uncomplicated percutaneous transluminal coronary angioplasty of a left anterior descending artery.

Case report

A 56 year old man with severe postinfarction angina unresponsive to medical treatment was investigated with a view to surgery. There were no detectable risk factors apart from previous heavy cigarette consumption of 60 per day. A resting electrocardiogram showed pathological Q waves in inferior leads. Stress testing on a bicycle ergometer showed 1 mm ST depression in leads II, III, and V4-V6 associated with

chest pain at 100 W. Stress thallium imaging showed a fixed inferior apical defect and reversible ischaemia in the diagonal and lateral territories. Cardiac catheterisation 18 months after infarction showed impaired left ventricular function with inferior hypokinesis and an ejection fraction of 34%. The right coronary artery was occluded near its origin with no antegrade or cross filling of distal branches. The circumflex system was non-dominant with only minor irregularities. The proximal left anterior descending branch was ectatic in part with a concentric stenosis of approximately 70% over a segment involving the origins of a septal branch and two diagonal branches, each measuring approximately 1.5 mm in diameter (Fig. 1a).

Percutaneous transluminal coronary angioplasty was performed using the femoral approach and a 3.7 mm balloon with an 0.016 inch flexible tipped wire Schneider-Medintag. The stenosis in the left anterior descending artery was crossed without difficulty. The transstenotic pressure gradient was 46 mm Hg falling to 6 mm Hg after three inflations at 8 atmospheres, each lasting 40 s. The procedure was not accompanied by chest pain, arrhythmia, or hypotension. Immediate repeat arteriography showed an improvement of the lesion with a 25% residual stenosis. There was non-opacification of the two diagonal branches (Fig.

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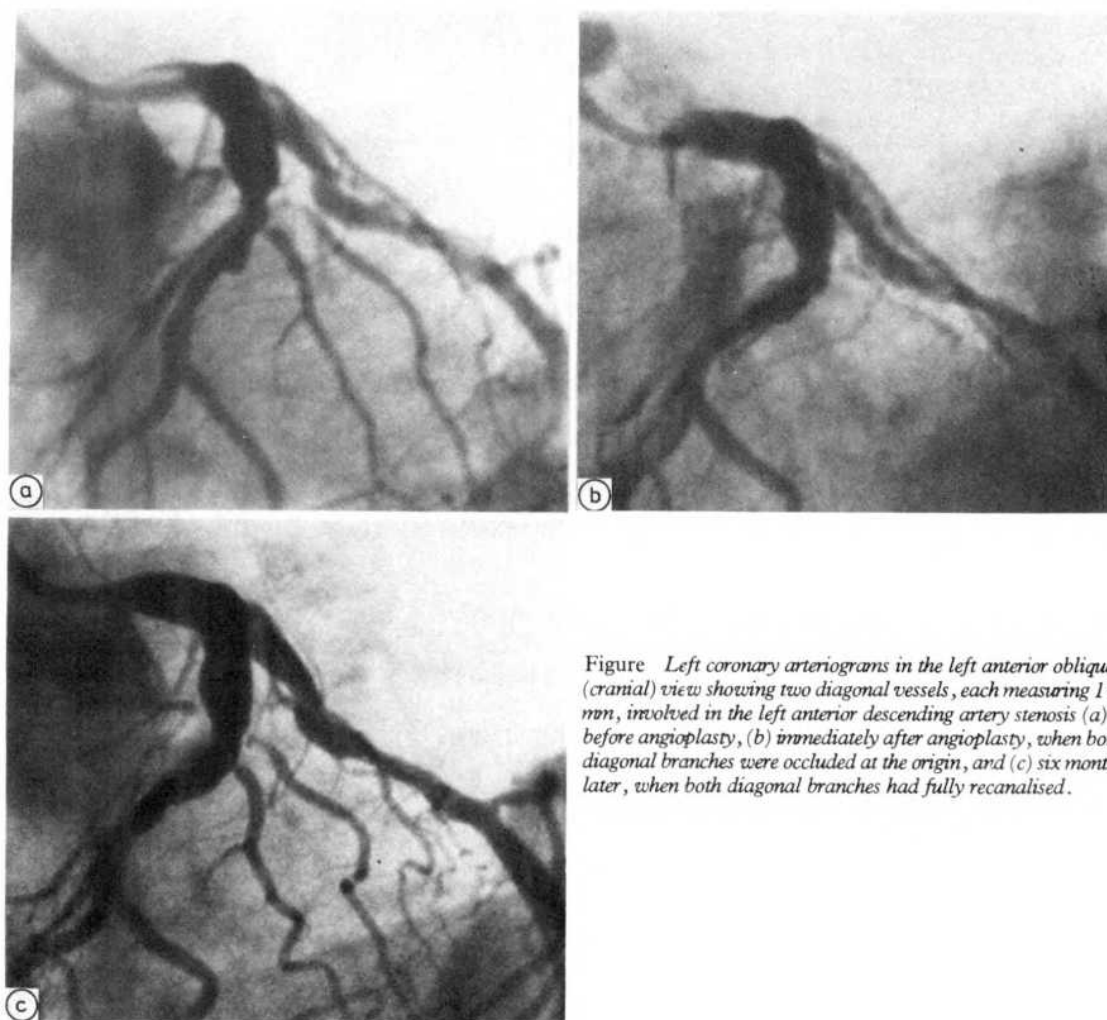


Figure Left coronary arteriograms in the left anterior oblique (cranial) view showing two diagonal vessels, each measuring 1.5 mm, involved in the left anterior descending artery stenosis (a) before angioplasty, (b) immediately after angioplasty, when both diagonal branches were occluded at the origin, and (c) six months later, when both diagonal branches had fully recanalised.

1b). The patient was given 10 000 units of heparin intravenously at the start of the procedure but no other anticoagulant. Aspirin was given on the day before the procedure and continued to be taken at 300 mg daily. Intracoronary nitrate 200 μ g was given before balloon passage and after each inflation up to a total dose of 1 mg.

The hospital stay was uneventful. A repeat electrocardiogram showed no changes over the next 48 hours. Plasma creatine kinase concentration rose from a preoperative value of 180 IU/l to a maximum of 302 IU/l 24 hours after the procedure with traces of cardiac isoenzymes. After discharge from hospital the patient reported mild anginal chest pain for two weeks

after operation. From the third week his symptoms disappeared despite increasing activity and withdrawal of all antianginal medications other than nifedipine 10 mg three times daily. Repeat exercise testing at three and six months showed an increased maximum capacity of 120 W with no subjective chest pain and no diagnostic ST-T changes in the anterior chest leads. Repeat thallium stress testing showed no reversible perfusion defects in the areas subtended by the anterior descending and diagonal vessels. A reperfusion image at four hours showed a fixed defect in the inferior region as before. Follow up coronary arteriography performed as a routine at six months showed no progression of the left anterior descending

stenosis. The two previously occluded diagonal branches were patent and appeared unchanged since before coronary angioplasty (Fig. 1c).

Discussion

The loss of a side branch as a result of coronary angioplasty is an important consideration in the selection criteria of patients for this procedure.² Most operators would avoid lesions involving side branches >2 mm in diameter since the occlusion of such vessels is likely to result in a clinical myocardial infarction. Meier *et al* have shown that side branches are rarely occluded unless they arise directly from the stenotic segment of the main vessel, when their origins are often diseased.¹ In such instances the occlusion rate was about 14%. The diagonal branches in our patient belonged to this category and were occluded as a result of an otherwise uncomplicated angioplasty of the main vessel.

The reappearance of the occluded side branches is the main interest in this report. Such spontaneous reappearances have not been previously documented but may have escaped notice if not specifically looked for at the time of follow up angiography. Spontaneous reappearance of vessels occluded in the course of the natural history of coronary artery disease is rare.³ The mechanism of vessel occlusion during angioplasty is probably different from the natural disease.^{4,5} Meier *et al* observed angiographic evidence of coronary dissection in a high proportion of their patients with branch occlusion and concluded that involvement of side branches by the dissection was the prime mechanism.¹ Other possibilities include coronary spasm, thrombosis, and redistribution of atheromatous plaque material.⁵ In our patient, careful review of the angiograms showed none of the usual features of coronary dissection such as an intimal cleft or vessel wall staining. Although dissection could not be excluded, it was probably unlikely. Similarly, coronary spasm cannot be ruled out, but the abrupt loss of both vessels at the point of their origins was more suggestive of an organic obstructive lesion. Such obstructions may be due to thrombus or atheromatous material. The last can be explained by the redistribution of atheromatous material from the adjacent left anterior descending vessel wall. The fact that the origins of the side branches were directly involved in the stenotic lesion meant that total occlusion can result from even a small amount of sequestered debris. Despite the transient occlusion of two side

branches our patient had a good clinical response to the angioplasty procedure. It is not possible to be dogmatic about whether the branch occlusion resulted in myocardial necrosis, but on balance it seemed unlikely.

The modest rise in cardiac enzymes with only traces of cardiac isoenzyme is often seen in otherwise uncomplicated cases. Our patient experienced no chest pain during his hospital stay, and there were no other clinical features of myocardial infarction. Our hypothesis is that occlusion was temporary and that early spontaneous recanalisation occurred leading to the improvement of anginal symptoms in the three weeks after the angioplasty procedure.

The most likely explanation for spontaneous recanalisation of the branches is reabsorption of atheromatous debris. Such clearing up of intraluminal debris has been suggested as one of the mechanisms by which coronary lesions continue to improve weeks after coronary angioplasty.⁴ It is not known what, if any, pharmacological agents would enhance this process. Oral anticoagulation has been shown to have no effect on the results of coronary angioplasty, and it was not used in this case.⁶ Our patient had the standard regimen of systemic heparinisation during operation, and treatment with aspirin 300 mg daily was started on the day of the procedure and continued afterwards. Further observations on spontaneous recanalisation of occluded side branches may help in our understanding of the healing process after vessel injury at coronary angioplasty.

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Fluid removal by haemofiltration in diuretic resistant cardiac failure

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SUMMARY A 60 year old woman with diuretic resistant cardiac failure was treated with intermittent haemofiltration before tricuspid valve replacement. This technique can remove large quantities of fluid rapidly, thus controlling oedema and allow appropriate fluid replacement. Haemofiltration is thus a simple and safe method of managing unresponsive oedema in cardiac failure sometimes allowing corrective cardiac surgery.

Some patients with severe cardiac disease continue to suffer from disabling pulmonary and peripheral oedema despite treatment with large doses of diuretic, inotropic, and vasodilative agents. Although the prognosis for such patients is often poor, life may be prolonged if the oedema can be relieved, allowing the patient to undergo definitive surgery. We report the use of intermittent haemofiltration for fluid removal in a patient with intractable cardiac failure.

Case report

A 60 year old housewife had diuretic resistant cardiac failure secondary to rheumatic heart disease. She had made an apparently complete recovery from an attack of rheumatic fever at the age of 13 years and was asymptomatic until left ventricular failure developed during pregnancy 10 years later. The cardiac failure responded to conventional treatment and the pregnancy continued successfully to term, after mitral valve disease had been diagnosed. Apart from minimal exertional dyspnoea she remained well for the next 15 years and required no treatment. Diuretics were prescribed after congestive cardiac failure had developed and cardiac catheterisation showed mixed mitral and aortic valve disease. By 1980 these symptoms had progressed and she underwent mitral valve replacement, aortic valvotomy, and tricuspid annuloplasty, which produced a pronounced initial improvement in her symptoms. Subsequently, however, she developed increasingly severe tricuspid regurgitation with dyspnoea at rest, hypotension (blood

pressure 90/50 mm Hg), and gross ascites, despite treatment with large doses of frusemide, amiloride, and metolazone. Several episodes of malaena occurred, which were thought to be due to mesenteric venous congestion, and her haemoglobin fell to 7 g/dl. Renal function was impaired with a plasma creatine concentration of 450 μ mol/l, a blood urea concentration of 20 mmol/l, and a creatinine clearance of 20 ml/min. Since she was too ill to undergo invasive cardiac investigations or cardiac surgery a decision was taken to correct her fluid overload by intermittent haemofiltration.

INTERMITTENT HAEMOFILTRATION

The right subclavian vein was cannulated by the Seldinger technique and a high flow dialysis catheter (Vas-cath, Gambro) was inserted and tunnelled beneath the skin. Blood was pumped at approximately 100 ml/min with a Sarns blood pump and extracorporeal blood lines through a 0.2m² haemofilter (Amicon 20) and returned to a peripheral vein. Clotting of the haemofiltration circuit was prevented by a bolus dose of heparin (2000 IU) given at the start of the procedure.

Haemofiltration was performed for four hours, removing 1200 ml/h, during which time pulse and blood pressure showed no significant change and arterial oxygen content increased from 8.0 kPa to 10.0 kPa. The procedure was repeated on two successive days with a net weight loss of 7 kg, and the patient was transfused up to a haemoglobin of 12 g/dl. Her clinical condition improved considerably and was accompanied by a pronounced reduction in cardiac size on chest radiograph. Cardiac catheterisation was therefore undertaken and confirmed the diagnosis of tricuspid regurgitation. A routine tricuspid valve

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replacement was performed, which was complicated by postoperative oliguria requiring supportive haemodialysis for two weeks. The oliguria resolved steadily, and at the time of discharge she was free of oedema and taking no diuretics; her creatinine clearance was 60 ml/min.

Discussion

Diuretic resistant oedema may be a serious problem in patients with cardiac failure. Peritoneal dialysis to remove fluid in these patients has been used for many years.¹ The efficiency of fluid removal is, however, poor, and in a patient with already compromised ventilatory function the splinting effect on the diaphragm may be detrimental. Haemodialysis is more efficient but is likely to be associated with life threatening arrhythmias and hypotension. In 1947, Alwall described the principle of ultrafiltration,² and its application to oedematous states was further explored by Silverstein *et al.*³

Isolated ultrafiltration relies on the circulation of blood through a conventional haemodialyser containing a Cuprophane membrane, with water and solutes being driven across it by hydrostatic pressure as in the human glomerulus. There is no contact with the dialysate. Although ultrafiltration is accompanied by less circulatory disturbance, complement activation still occurs. This results in leucocyte and platelet aggregation, which may cause pulmonary microembolisation and severe hypoxaemia.

With the development of complex, biocompatible membranes made of polycarbonate, the technique of haemofiltration became possible. Unlike the Cuprophane membrane used in ultrafiltration, these newer membranes have an extremely high permeability to water and solutes and produce minimal leucocyte and platelet clumping.⁴ The potential advantages of haemofiltration and ultrafiltration in the management of acutely ill oliguric patients were quickly realised⁵ and also applied to the correction of hypertension and fluid overload in chronic renal failure.⁶

The extracorporeal circuit for haemofiltration is quick and easy to establish. If one of the lines is placed in an artery a blood pump is unnecessary, thus reducing the potential risks of haemorrhage and air embolism. Our experience with this technique now extends to over 30 patients, in whom no serious complications of the procedure have occurred. These patients had developed acute fluid overload either because of acute renal failure or because of underlying cardiovascular disease. Intermittent haemofiltration was used to control pulmonary oedema, improve oxygenation, and make intravascular space for the administration of intravenous antibiotics, inotropic agents, blood products, or parental nutrition. We have also successfully used haemofiltration during orthotopic cardiac transplantation to remove pulmonary and peripheral oedema, as described previously during cardiopulmonary bypass.⁷

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Permanent pacemaker failure due to surgical emphysema

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SUMMARY A 76 year old man developed a left pneumothorax after implantation of a permanent endocardial pacemaker via the left subclavian vein. The resulting surgical emphysema caused temporary failure of the pacing system.

Permanent pacing systems that use a unipolar electrode require close contact between the pulse generator and surrounding tissues to complete the pacing circuit. Occasionally, electrode insertion via the subclavian vein is complicated by puncture of the lung apex causing a pneumothorax. We report a patient who developed a pneumothorax immediately after insertion of a permanent pacemaker.

Case report

A 76 year old man presented in August 1984 with a three week history of dizziness and dyspnoea on exertion. Physical examination showed mild congestive cardiac failure with a heart rate of 30 beats/min, and the electrocardiogram confirmed the presence of complete heart block. There was no previous history of cardiac or pulmonary disease. Temporary pacing with a bipolar electrode, positioned in the apex of the right ventricle via the right subclavian vein, resulted in rapid clinical improvement.

Two days later a permanent pacing system was implanted under local anaesthesia. A Siemens unipolar tined electrode was introduced into the right ventricular apex via the left subclavian vein. Some difficulty was experienced with the venous cannulation, and the left lung apex was punctured during the procedure. A satisfactory electrode position was, however, achieved, and the unit immediately functioned well with a pacing threshold of 0.3 V and an impedance of 528 Ohm. The pulse generator, a

Biotronik Leptos MO1/2B, was positioned in a left pectoral subcutaneous pocket. The temporary electrode was left in situ.

Shortly after returning to the ward he became dyspnoeic with clinical signs of a left pneumothorax, which was confirmed by x ray examination. An intercostal drain was inserted in the mid-axillary line and the lung expanded promptly. Three days later the permanent pacemaker suddenly failed with loss of the pacing artefacts on the electrocardiogram. A moderate amount of surgical emphysema had developed in the left anterior chest wall (Fig. 1), and crepitations were palpable around the pulse generator. Application of light pressure over the generator resulted in the immediate return of ventricular pacing, which ceased when the pressure was released (Fig. 2). Heart rate was maintained with the temporary pacemaker for a further four days, by which time the surgical emphysema had resolved and the permanent system resumed normal function. The intercostal drain and the temporary electrode were removed, and recovery was thereafter uneventful.

Discussion

Permanent pacemakers that use unipolar electrodes require good contact between the pulse generator and the pocket to complete the pacing circuit. Pacemaker failure in this case was caused by air collecting around the pulse generator, isolating its earthplate from the surrounding tissues. When pressure was applied over the generator this air was displaced, the circuit was completed, and pacing reinstituted. We are not aware

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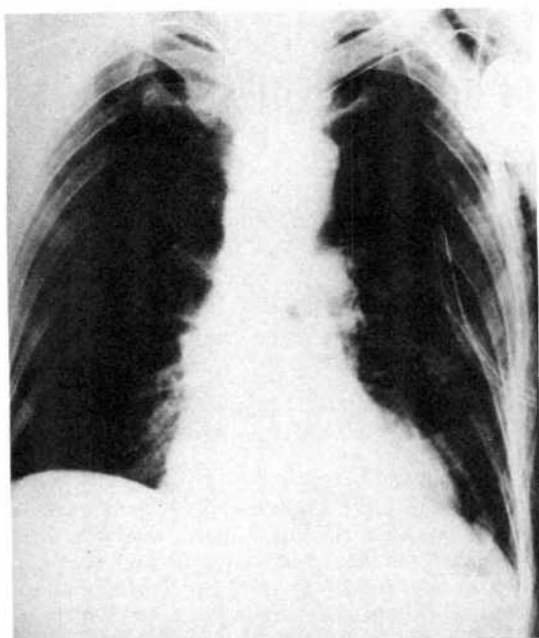


Fig. 1 x-ray film showing the position of the chest drain and pulse generator and the surrounding surgical emphysema.

of any previous reports of permanent pacemaker failure attributed to this cause.

Even in the most experienced hands pneumothorax occurs in up to 5% of patients after subclavian cannulation,^{1,2} and so it is likely that this type of problem will occur again. We would recommend therefore that

a temporary electrode be left in situ after permanent pacemaker insertion if the subclavian cannulation proves difficult and pulmonary damage is suspected.

Pacemaker failure in the early postoperative period is usually caused by electrode displacement, which requires further surgical intervention. If, however, permanent pacemaker failure with loss of pacing artefacts occurs in the presence of surgical emphysema then a conservative approach to management is indicated. Pacemaker function is likely to return as the emphysema resolves. In our patient air was able to enter the pulse generator pocket by tracking along the tissue plane from which the pocket had been formed. The risk of developing this complication may not be so great when healing has occurred and the generator is encapsulated in fibrous tissue but it cannot be entirely discounted. All permanent pacemaker dependent patients who develop surgical emphysema near the pulse generator at any time, and from any cause, should, therefore, be closely monitored for this type of pacemaker failure.

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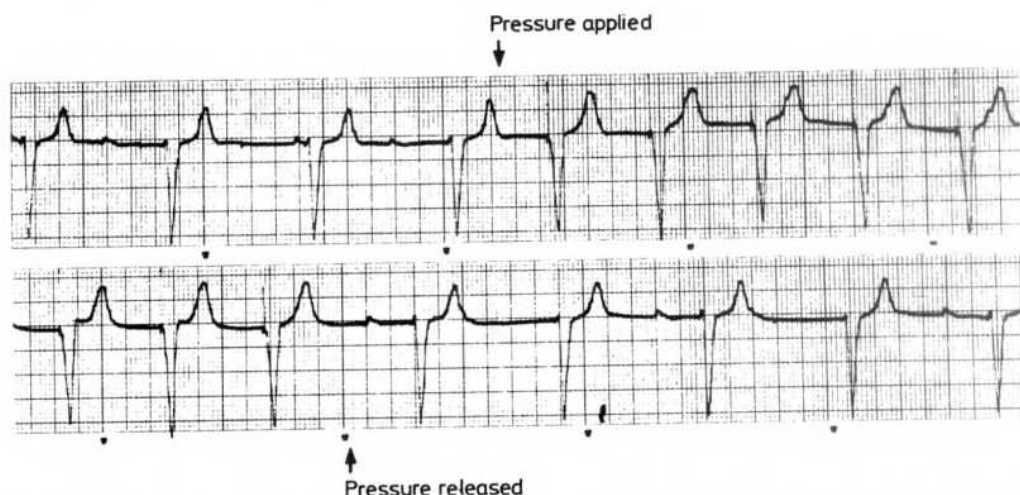


Fig. 2 Electrocardiogram showing the effect of pressure on the pulse generator. Before and after pressure is applied the rate is maintained at 50 beats/min by the temporary pacemaker with no visible pacing artefact from the permanent system. While pressure is applied the permanent box works normally at a rate of 70 beats/min.

Chronic nicotine ingestion and atrial fibrillation

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SUMMARY Paroxysmal atrial fibrillation occurred in a fit 35 year old man who consumed large doses of nicotine chewing gum (Nicorette Leo) over a prolonged period.

Nicotine chewing gum was developed as an aid to smoking withdrawal and is usually effective in a dose of eight 2 mg pieces daily.¹ Reports of the cardiovascular effects of nicotine gum have been limited to an increase in heart rate,² although nicotine has been shown to cause arrhythmias in animals.³ We report a patient who developed atrial fibrillation while consuming three to four times the usual amount of nicotine chewing gum.

Case report

A 35 year old man was admitted to hospital as an emergency, having been woken with prolonged periods of irregular palpitation. He denied chest pain or breathlessness but gave a one month history of similar periods of palpitation of shorter duration. For 18 months he had been trying to stop smoking (previously 40 cigarettes per day) and had been prescribed nicotine chewing gum (Nicorette Leo). Initially, he consumed 20 pieces of the 2 mg gum daily, but two months before admission he had stopped smoking completely and increased his consumption to 30, 2 mg pieces, chewing each gum for at least 20 minutes. He chewed the gum almost continually. He drank one bottle of wine a day but did not drink spirits. There was no past history of rheumatic fever or scarlet fever and no family history of ischaemic heart disease or hyperlipidaemia.

On admission he was in atrial fibrillation with an apical rate of 150 beats/min but was normotensive and had no signs of cardiac failure. He had no cardiac murmurs or pericardial friction rub, was clinically euthyroid, and remained afebrile throughout admission.

He was given digoxin and 24 hours later had reverted to sinus rhythm. Digoxin was stopped 24 hours later. On three consecutive days the electrocardiogram and serum aspartate aminotransferase and lactate dehydrogenase activities were normal. Serum thyroxine and tri-iodothyronine concentrations, and thyrotropin releasing hormone stimulation test were normal, as were chest x-ray films, echocardiograms, full blood count, erythrocyte sedimentation rate, plasma electrolyte concentrations, serial viral titres, and fasting concentrations of glucose, cholesterol, and triglycerides. The patient also had a normal exercise test (Bruce protocol) with no evidence of myocardial ischaemia. Plasma γ glutamyl transferase activity was moderately increased at 90 u/l (normal 10-55 u/l), but bilirubin concentrations and serum alanine aminotransferase and alkaline phosphatase activities were normal. Blood nicotine concentration five hours after waking with palpitation (14 hours after the last Nicorette gum) was 4.8 ng/ml.

He was reviewed at one, two, six, and 12 months, during which time he abstained from cigarette smoking and Nicorette consumption but continued to drink one bottle of wine a day. At one month a 24 hour ambulatory electrocardiogram was normal and at six months blood nicotine was undetectable, the plasma γ glutamyl transferase activity remaining unchanged at 100 u/l. To date he has had no further episodes of palpitation.

Discussion

The temporal relation between Nicorette (Leo) consumption and palpitation in our patient suggests a causal link between the two. He may have been predisposed to arrhythmias by drinking a bottle of wine a day, but his consumption of alcohol and the plasma γ glutamyl transferase activity did not change over a 12

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month follow up period when he was free of palpitation.

After chewing nicotine gum the peak blood concentration of nicotine is no higher than after smoking cigarettes.¹ Even in habitual smokers, however, blood nicotine is undetectable eight hours after stopping smoking.⁴ In contrast, we detected nicotine in our patient 14 hours after chewing his last piece of nicotine gum. Thus a day to day accumulation of nicotine appears to be a potential risk when nicotine gum is chewed in large quantities. The effects of long term nicotine poisoning in man are unknown,⁵ but it is possible that atrial fibrillation in our patient was a manifestation of chronic nicotine intoxication.

We thank Dr R F Robertson, Royal Infirmary, Edinburgh, for allowing us to report his patient and Dr

Colin Feyerabend, for performing nicotine assays.

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Changing echocardiographic features of a hydatid cyst of the heart

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SUMMARY A 24 year old woman with pulmonary embolism and a past history of echinococcal disease underwent echocardiography which detected two cysts in the right ventricle which became more solid after treatment with mebendazole. The surgical and pathological findings confirmed the presence of the two cysts and the hydatid nature of the lesion.

Echinococcus disease is common in many parts of the world and affects the heart in 0.5–2% of cases.¹ Major complications result almost always from rupture of the cysts either in the pericardium or in the heart chambers. Death may occur from anaphylactic shock, cardiac tamponade, acute pulmonary embolism, subacute or chronic pulmonary hypertension,² systemic embolisation especially in the central nervous system, or secondary generalised hydatidosis. To allow preventive surgical treatment to be undertaken the diagnosis must be made before such complications occur. Although there are few reports of the detection of hydatid cyst of the heart by echocardiography,^{3–5} the present case illustrates the value of this procedure in diagnosing hydatid cyst of the heart and describes the changing echocardiographic features of the disease.

Case report

A 24 year old Moroccan woman was admitted at 36 weeks' of pregnancy because of pulmonary embolism. She had emigrated from Morocco four years before admission. Three years previously she had been admitted to the same hospital, where the diagnosis of pulmonary hydatid disease had been made. She refused surgical treatment and received a course of treatment with mebendazole. Her pregnancy was normal until the thirty sixth week when she was admitted because of the sudden onset of haemo-

ptysis, cough, dyspnoea, and sharp right chest pain aggravated by deep breathing.

On admission physical examination showed tachypnoea, tachycardia, and peripheral cyanosis. Clinical examination of the heart was normal, as was the electrocardiogram. Chest radiographs showed multiple round pulmonary shadows in the left lower and right upper lobes. Pulmonary embolism was confirmed by ventilation-perfusion radionuclide images but femorocaval phlebography failed to detect thrombosis.

To investigate a possible cardiac cause for pulmonary embolism, echocardiography was performed using a mechanical sector scanner (ATL) with a 3 MHz transducer. Cross sectional echocardiography detected two echo free areas (1.0 cm × 1.5 cm and 0.5 cm × 1.0 cm) indicating the presence of cysts in the inferior wall of the right ventricle. The best images were obtained in the apical four chamber and sub-costal view (Figure a).

A six week trial course of mebendazole 4 g daily was given and at the end of the medical treatment, a further echocardiogram was recorded (Figure b). Although the two echocardiographic views are not strictly identical (partly because of right ventricular enlargement secondary to pulmonary hypertension which developed meanwhile) the different appearances indicate a change in the nature of the hydatid cyst. Since hydatid material was probably still present, surgical treatment was undertaken. Two cysts with evidence of partial rupture were excised, and pathological examination confirmed the presence of hydatid material.

Requests for reprints to Dr Willy Kostucki, Department of Cardiology, Hôpital Universitaire Saint-Pierre, Rue Haute 322, B - 1000 Brussels, Belgium.

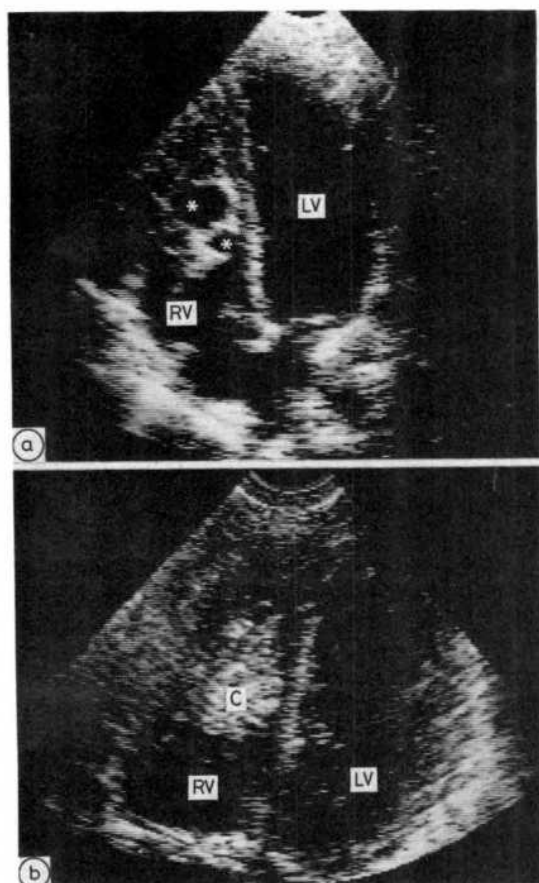


Figure Cross sectional echocardiograms obtained from a slightly modified apical four chamber view showing (a) the bilobulated cyst (*) located in the right ventricle (RV) and (b) the cyst (C) filled with echodense material six weeks later. The right ventricle is dilated. LV, left ventricle.

Discussion

This unusual case of pulmonary embolism secondary to a hydatid cyst of the right ventricle illustrates the fact that hydatid cyst of the heart is rarely diagnosed clinically, even in a patient with echinococcal disease,

because of the lack of specific clinical and radiological features. If this condition is, however, suspected echocardiography is the method of choice in its diagnosis. This report demonstrated the ability of echocardiography to detect two cysts in the right ventricle. The cross sectional echocardiographic differential diagnosis of a cystic lesion includes hydatid cyst of the heart and the very rare cystic teratoma.⁶ Nevertheless, hydatid cyst of the heart may also resemble a tumour like lesion echocardiographically. The echocardiographic evidence of a cystic hydatid lesion changing into a filled cyst has been reported only in association with hydatid cysts of the lungs and liver, which are probably due to the detachment of the germinative membrane suggesting an involution of the parasite after chemotherapy.⁷

Although this case seems to indicate the effectiveness of high doses of mebendazole in the treatment of hydatid cyst of the heart, we do not believe that this treatment would have prevented further rupture of the cyst and embolisation of the hydatid material, which, even if aseptic, would in this case have increased the pulmonary hypertension. Surgery remains the treatment of choice.

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Correspondence

Pathways of preferential arterial conduction

Sir,

In his reply to our earlier letter (1985; 53: 350) it seems to us that Dr T N James has misconstrued the point we wish to make. In our letter it is clear that when we speak of the division of the ventricular bundle branches we discuss the division of *all* the bundle branches. The relevant sentence is "if the tissue within the insulated sheaths is divided". Here we use the plural "sheaths" and clearly refer to the entirety of the bundle branches. Dr James's comments concerning the division of an individual bundle branch are entirely appropriate. To the best of our knowledge, however, if all the bundle branches are divided (in the absence of any pathways for pre-excitation) then conduction into the ventricle does indeed cease. In other words, division of an anatomically discrete system will

prevent the conduction. We restate our contention that this is not the case with the atrial myocardium; this is the point that we asked Dr James to answer.

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Academisch Medisch Centrum,
Meibergdreef 9,
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Notices

35 years of electrocardiology in Amsterdam

An international symposium honouring the late Professor Dirk Durrer and sponsored by the Interuniversity Cardiology Institute in The Netherlands will be held in Amsterdam on 29 and 30 May 1986. Further information may be obtained from: Stichting "DURRER-Comité", Secretariaat: Mevr. B. Hoogenhout, Assumburg 50, 1081 GC Amsterdam, The Netherlands.

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts will be 1 August 1985.

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Editorial: digitalis: where are we now? <i>D A Chamberlain</i>	227	Usefulness of plasma renin activity in predicting haemodynamic and clinical responses and survival during long term converting enzyme inhibition in severe chronic heart failure: experience in 100 consecutive patients <i>M Packer, N Medina, M Yushak, W H Lee</i>	298
Drug treatment of heart failure <i>C T Dollery, L Corr</i>	234		
Changing digoxin potency and cardiac mortality in England and Wales 1968-76 <i>H Tunstall-Pedoe</i>	243	Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state <i>J G F Cleland, H J Dargie, S G Ball, G Gillen, G P Hodsman, J J Morton, B W East, I Robertson, I Ford, J I S Robertson</i>	305
Rapid plasma digoxin assay in outpatients—a useful routine technique? <i>J Savill, M Mitchell, D Wood, D M Krikler</i>	248		
Withering bicentennial celebrations	251	Acute haemodynamic and metabolic effects of dopexamine, a new dopaminergic receptor agonist, in patients with chronic heart failure <i>J R Dawson, D S Thompson, M Signy, S M Juul, P Turnbull, B S Jenkins, M M Webb-Peploe</i>	313
Bicentenary of <i>An Account of the Foxglove</i> <i>A G W Whitfield</i>	253		
Withering and the foxglove: the making of a myth <i>D M Krikler</i>	256	Respiratory gas exchange in the assessment of patients with impaired ventricular function <i>D P Lipkin, J Perrins, P A Poole-Wilson</i>	321
Plants and cardiac glycosides <i>A Hollman</i>	258		
Cultivation and breeding of <i>Digitalis lanata</i> in the Netherlands <i>C Mastenbroek</i>	262	Case reports Hypertrophic cardiomyopathy simulating an infiltrative myocardial disease <i>A Frustaci, F Loperfido, F Pennestri</i>	329
Left ventricular aneurysm: the Wessex experience <i>D J M Keenan, J L Monro, J K Ross, J M Manners, N Conway, A M Johnson</i>	269	Management of aortic left ventricular tunnel <i>P Ribeiro, L B Bun-Tan, C M Oakley</i>	333
Valvar prosthetic dysfunction: localisation and evaluation of the dysfunction using the Doppler technique <i>C Veyrat, S Witchitz, A Lessana, A Ameur, G Abitbol, D Kalmanson</i>	273	Right atrial spleen <i>P Kuijter, R Dion, F van Merrienboer</i>	337
Balloon valvuloplasty and angioplasty in congenital heart disease <i>G A H Miller</i>	285	Early prenatal detection of double outlet right ventricle by echocardiography <i>P A Stewart, J W Wladimiroff, A E Becker</i>	340
Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease <i>D E Stewart, H Ikram, E A Espiner, M G Nicholls</i>	290	Notice	342

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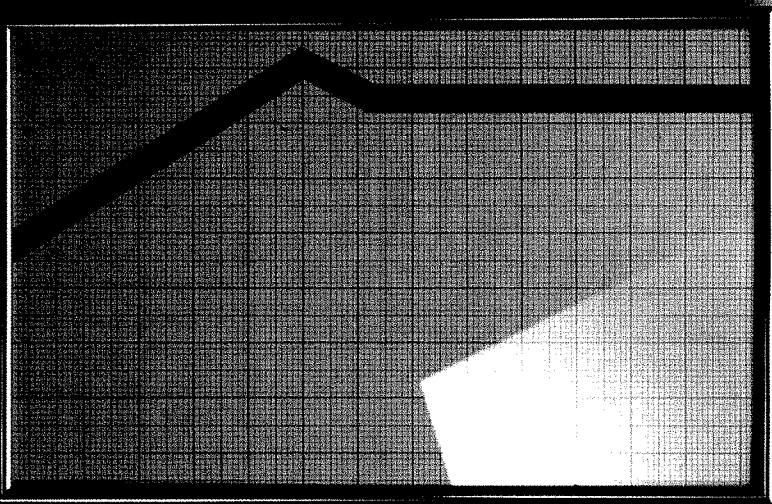
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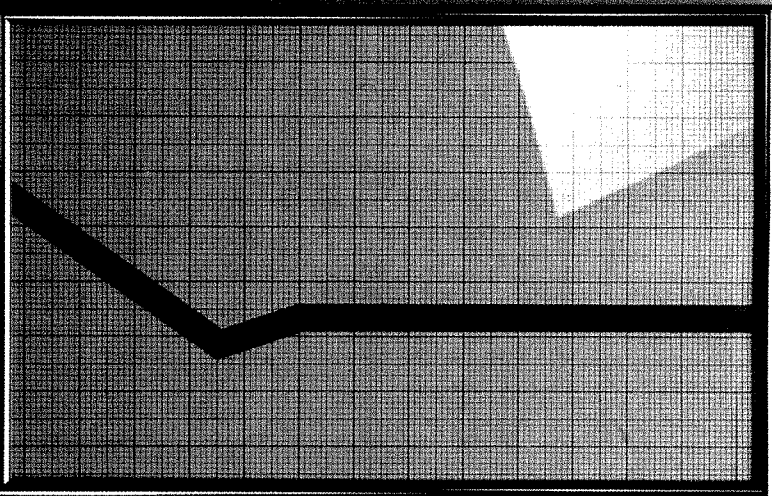
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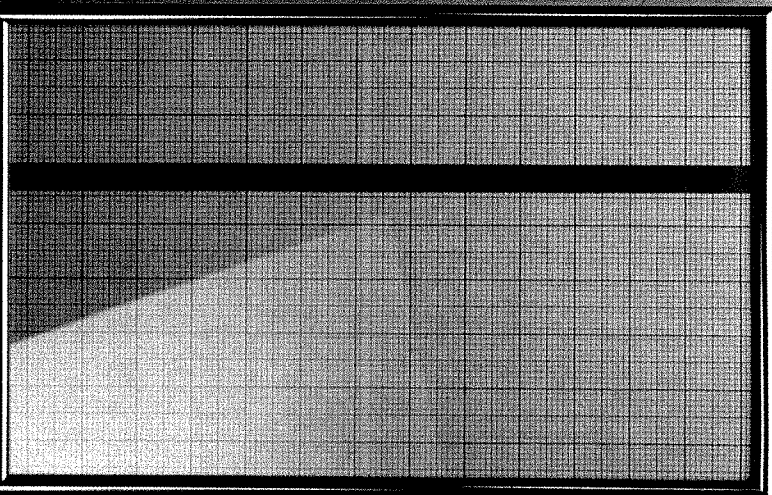
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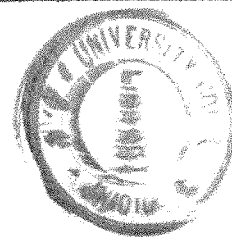
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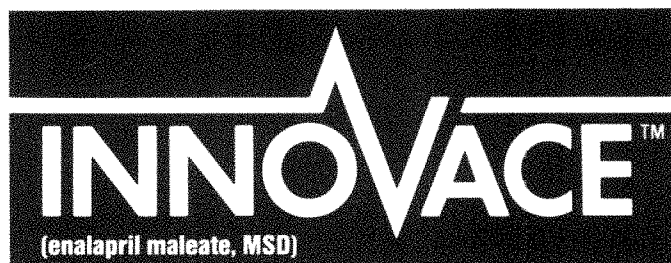
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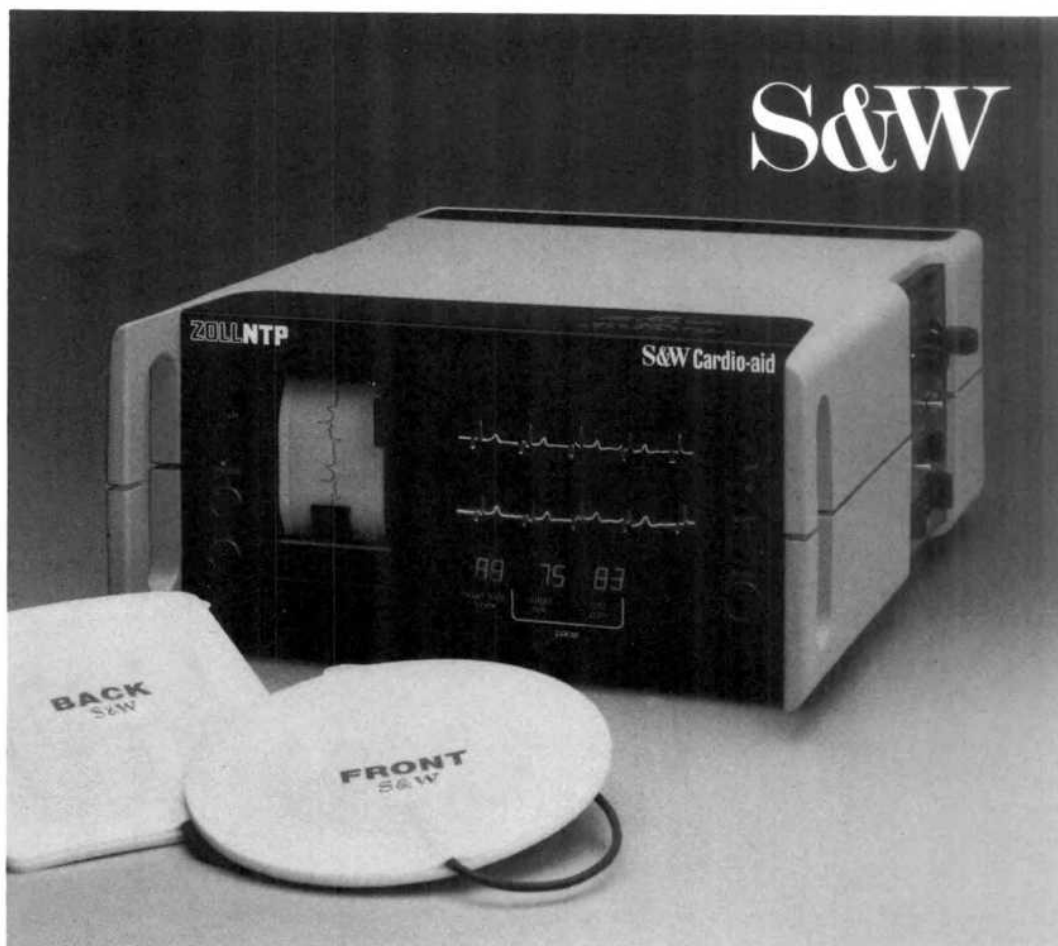
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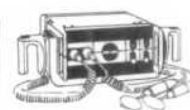
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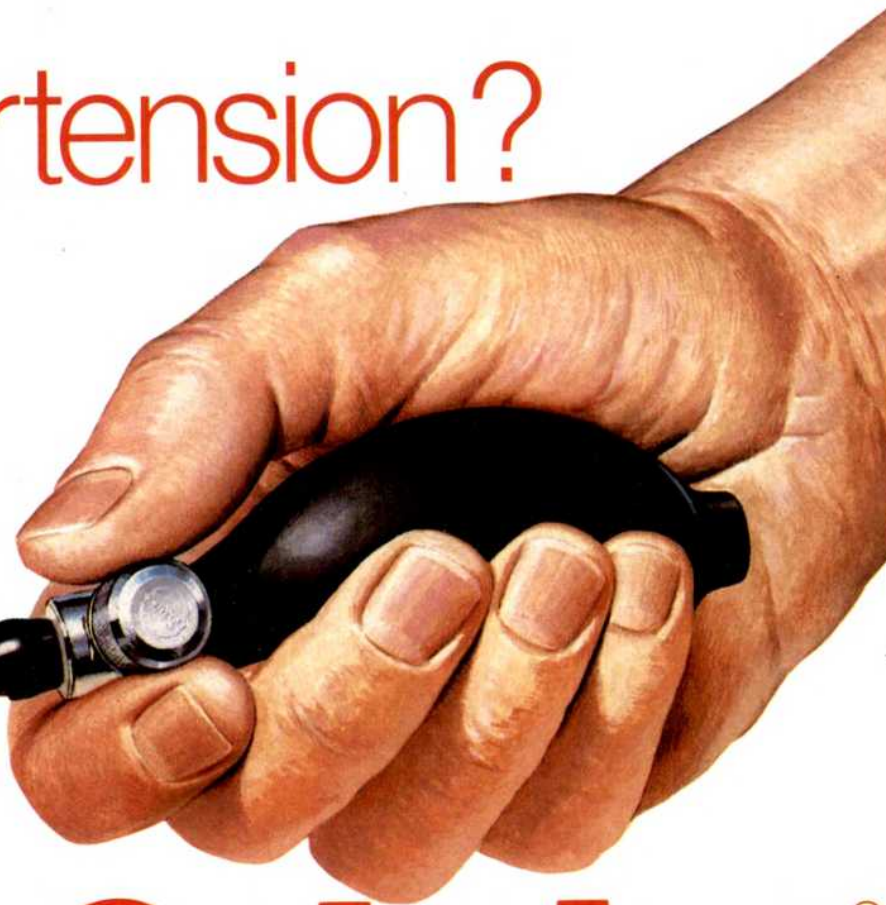
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... Time will fix the real value on this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind.

William Withering¹

Digitalis can still arouse controversy and even passion, but none can deny that it has passed the test of time perceived by Withering as a prime marker of value. Few opportunities will ever arise to celebrate the bicentenary of a drug, for what others will last the course? But digitalis has not done so with an untarnished reputation—problems have been apparent from the outset. Withering himself was concerned that digitalis might “be regarded as dangerous and unmanageable” if his advice on usage went unheeded.

This early warning on the hazards of digitalis toxicity received less attention than it merited, though the picture became clear only with hindsight. Even now we cannot know how the balance would look if the accrued benefit of 200 years could be weighed against the unintended harm. Major advances in the pharmacodynamics and pharmacokinetics of the drug in the past two decades now mean that science can replace empiricism. Now (with new knowledge combined with old but valid precepts) we should be able to use digitalis more judiciously, more safely, to better effect, but perhaps less widely than in the past. Withering would be content with that.

The actions of digitalis

Digitalis is a drug with an unlikely profile. It stimulates the myocardium while depressing sinoatrial and particularly atrioventricular nodal function; these apparently disparate actions match exquisitely the

requirements for treating patients with atrial fibrillation and heart failure.

The mechanisms by which these effects are achieved are complex, but at cellular level they relate principally to inhibition of sodium-potassium adenosine triphosphatase.² Some adenosine triphosphatase related effects, notably those on contractility, are mediated directly by changes in ionic concentrations across cell membranes. Others, principally the electrical ones, follow more from modulation of the autonomic system. Increased vagal activity and the sensitivity of the sinoatrial and atrioventricular nodes to such activity are most important—sympathetic influences are reduced at therapeutic doses and increased when toxic concentrations are reached.³ The nodes have little direct response, as can be demonstrated by modest or inconsistent changes after transplantation⁴ or pharmacological blockade.⁵ Some of the therapeutic effects of digitalis in heart failure depend also upon changes in peripheral venomotor tone.⁶

Commonly used cardiac glycosides

Digitalis leaf in the tablet form is now of mainly historical interest. Digitoxin, ouabain, digoxin, medigoxin, and lanatoside C are the preparations used in Britain to greater or lesser degree. They have widely disparate pharmacokinetics. Not all the differences are sufficiently recognised, though they have been well described in authoritative reviews.⁷

Digitoxin is the most important constituent of *Digitalis purpurea*. In its modern purified form it deserves a more prominent role among the cardiac glycosides. Digitoxin is rapidly and fully absorbed after oral administration. Over 90% of the glycoside present in plasma is bound to albumin but only the free fraction exchanges readily with tissue sites. The ratio of myocardial to plasma concentration is less than 10:1. Metabolism is important, since at least 50% of administered digitoxin undergoes transformation in the liver; some of the resulting com-

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pounds retain cardioactivity. Digitoxin and most of its metabolites are excreted in the bile, but the parent compound is absorbed again in the enterohepatic cycle. This and the avid protein binding that permits only limited renal excretion account for the relatively long plasma half life—nearly five days even with normal hepatic function. Loss in the faeces and urinary excretion both of digitoxin and its metabolites ultimately account for elimination.

Ouabain (strophanthin G) is found in *Strophanthus gratus* and is a glycoside related to digitalis. Gastro-intestinal absorption is poor and unreliable; administration must therefore be intravenous. Haemodynamic effects occur more rapidly than with digoxin and peak effects are obtained within two hours. Elimination is also faster (plasma half life of about 18 hours) and mostly renal, though the drug is also lost through the gut.

Digoxin is obtained from *Digitalis lanata*. It is incompletely absorbed; on average about 70% enters the circulation. In the past, tablet brands and even batches differed widely in the bioavailability of their digoxin content. Changes in manufacture of Lanoxin in 1969 and 1972, leading first to a reduction in bioavailability and then to an increase,⁸ prompted an appraisal of the variation between brands. Such differences were of considerable clinical importance⁹ and potentially dangerous¹⁰ yet had remained unknown until that time. A new standard for dissolution rate has led to acceptable uniformity and much greater safety. Differences in capacity for absorption between individuals are usually slight. Though the process is susceptible to interference (see below), timing of dosage in relation to meals makes only a small difference. About 10% of digoxin in plasma is protein bound. The ratio of myocardial to plasma concentration is approximately 100:1. Digoxin is not metabolised after absorption. But metabolism by micro-organisms may occur within the bowel after ingestion.¹¹ *Eubacterium lentum*, an anaerobic saprophyte, can inactivate digoxin by reduction of the lactone ring of the molecule and is responsible for the apparent resistance to the effects of the drug in a minority of individuals. The potential for drug toxicity is increased in subjects harbouring this organism since abrupt changes in gut flora, such as occur with antibiotic treatment, may restore the full potential for glycoside absorption. Digoxin is eliminated principally by the kidney. The key role of renal function in the rate of elimination of digoxin became clear when the pharmacokinetics of tritiated digoxin were investigated.¹² Toxicity must have been very common in patients with impaired renal function before this important fact was recognised. Even now some hazard remains, since many patients are given empirical doses of the glycoside

when the state of their renal function is quite unknown.

Medigoxin is beta-methyl digoxin. This preparation is absorbed more readily than digoxin and is subsequently converted to it. Though better absorption implies less variation in bioavailability, the drug has not found wide favour in Britain.

Lanatoside C is obtained from *Digitalis lanata*. Absorption is poorer than that of digoxin; conversion to digoxin occurs, mainly in the gut.¹³ Intolerance to digoxin is therefore not a rationale for using this glycoside. Variation in bioavailability must be greater than with digoxin, in keeping with the principle that the poorer the absorption of a drug the greater the potential for variation.

Do glycosides improve heart failure?

No physician will dispute the value of cardiac glycosides in slowing the ventricular rate of patients with atrial fibrillation and preventing many instances of supraventricular tachycardia. These arrhythmias may promote or exacerbate heart failure and in such cases digoxin may have an important controlling effect.

The value of digitalis in heart failure with sinus rhythm is more contentious. Most of the evidence for an important inotropic effect relates to the acute heart failure. Early experimental observations^{14,15} were followed by clinical measurements of increased contractility; one of the most convincing was based on force velocity curves obtained by means of radio-opaque markers sewn on to the myocardium at operation.¹⁶ Shifts in these curves with ouabain treatment indicated a positive inotropic effect but some were associated with slight falls in cardiac output. These falls are now known to depend on reflex adjustments of venous return and peripheral resistance but they have been incorrectly interpreted as denying the possibility of clinical benefit. Non-invasive measurements of systolic time intervals confirm a positive inotropic action both for subjects with normal hearts¹⁷ and those with heart failure.¹⁸ Though favourable changes in cardiac output are not found at rest, differences may be observed during exercise.¹⁹ The paucity of exercise data reflects the greater difficulty in making meaningful observations in a complex system replete with possibilities for autoregulation. Overall, the balance of evidence rests heavily in favour of digitalis augmenting contractility acutely, both in the presence of normal ventricular function and in heart failure.

The evidence for a persistence of benefit in chronic heart failure should be examined separately from that relevant to acute failure. Data from the latter are often extrapolated to chronic heart failure,

but the notion has rarely been addressed; indeed clinical and laboratory experiments to prove or refute it are difficult to devise. Some information on duration of effect is available, however. An ingenious method of assessing an index of contractility was described by Davidson and Gibson.²⁰ The acceleration of the ball inside the Starr-Edwards valve can be measured non-invasively; by this technique the augmented power of contraction after acute digitalisation diminished rapidly after only a few hours. On the other hand Griffiths and colleagues adduced evidence from studies with M mode echocardiography and systolic time intervals that the inotropic effects of digoxin had diminished six weeks after long term maintenance digoxin had been discontinued compared with observations made during treatment.²¹ Arnold and colleagues drew similar conclusions from haemodynamic measurements.²² An index of heart failure based on a complex combination of clinical and radiographic observations was also lowered by digoxin in a placebo controlled trial.²³ Even if digitalis does exert a continuing positive inotropic effect during sustained use, the action may not be apparent subjectively. Several studies attest to the lack of any observable deleterious effect when the drug is discontinued.^{24,25} But subtle changes of importance during exercise or in maintaining compensation under critical conditions could easily be missed by simple clinical observations. In summary, we do not know whether cardiac glycosides can exert a useful sustained effect in the treatment of chronic heart failure.

Measurements of plasma concentrations of digoxin and digitoxin

For most of the 200 years that digitalis has been in common use its clinical pharmacology was poorly understood because plasma and tissue concentrations could not be measured. But once isotopically labelled glycoside became available rapid progress was made in pharmacokinetic studies, and the crucial importance of renal function in digoxin therapy became apparent.

Reliable measurements in patients on maintenance therapy followed the introduction of radioimmunoassay in 1969.²⁶ Most therapeutic concentrations of digoxin are in the range 1–2 µg/l (1.28–2.56 µmol/l), but lower concentrations will suffice if, for example, atrioventricular nodal function is already impaired so that only a small additional effect is needed to control heart rate satisfactorily. Concentrations of digitoxin tend to be 10 to 15 times higher because of the greater protein binding of the drug. Samples for both assays are best taken when plasma concentrations have reached a

relatively steady state after drug ingestion, that is about six to eight hours after the last dose. After this results may be misleadingly low.

Measurements of plasma concentrations are not needed in most patients on maintenance therapy. Certainly they do not automatically provide an answer for achieving an optimal dose since complex relations between the drug, the state of the cardiac tissues, and the many metabolic and therapeutic interactions at cellular level all combine to create a wide range of possible therapeutic concentrations within which only a narrow band may be appropriate for one individual or for one individual at a given time. Even the newly available rapid plasma digoxin assay should not replace careful chemical monitoring for dose selection in the majority of patients.²⁷ But measurements may be useful as a guide to the diagnosis of toxicity and in investigating apparent failures of response (especially when unusually large doses of glycoside are administered). Assays are of great value in pharmacokinetic research.

Other limitations of plasma concentrations must be recognised. Carelessness in defining the interval between dose and sampling can cause misleading results. Spurious values have been reported as a result of cross reactions from an antibody of unsatisfactory specificity in the presence of other drugs²⁸ and from cross reactions from unknown substances in patients with liver disease,²⁹ renal impairment,³⁰ and in premature infants.³¹

Unwanted effects and toxicity of digitalis

Efficacy is not the sole consideration when judging the value of a drug; beneficial effect must always be balanced against toxicity and unwanted effects. The load of adverse effects with digitalis is weighty; toxicity is common even during use by skilled and cautious physicians. The reasons are manifold. First, the differences in plasma or tissue concentrations associated with optimal beneficial effect or with toxicity are small; they may even overlap.³² Secondly, variations in absorption, metabolism, or excretion of glycosides cannot readily be assessed; thus the precision with which plasma concentrations can be predicted is unsatisfactory. Thirdly, individuals show appreciable variation in the sensitivity of some tissue responses to cardiac glycosides; a plasma level inadequate for one patient may be excessive for another. This is true for example, of conductivity within the atrioventricular node.³² Finally, abrupt changes in response can occur as a result of drug interactions.

With this catalogue of problems, unwanted effects must be frequent. Hurwitz and Wade drew attention to the problem in 1969 when they found 20% of patients on maintenance therapy had unwanted

effects.³³ This could have been ascribed to the carelessness of outpatient prescribing, but in 1971 Evered and Chapman made similar observations on patients in a British hospital³⁴ as did Beller and colleagues in an American one³⁵; these later studies were supported by newly available assays for plasma glycoside concentration. Perhaps significantly, a study of patients treated exclusively with digitoxin showed only a 5% prevalence of toxicity.³⁶ Absorption and elimination of this glycoside are relatively consistent; since plasma concentrations must be more predictable, digitoxin may perhaps be safer than digoxin, though it would be difficult to prove this assertion.

The clinical manifestations of digitalis toxicity are believed to depend on two interacting mechanisms. The first is related to the effect of plasma concentrations on the central nervous system, and includes not only the familiar side effects of nausea, vomiting, and altered vision but also those cardiac effects due to increased vagal tone. These tend to be very distressing but rarely dangerous. The second mechanism depends on tissue concentration and is related to the increased automaticity of subsidiary cardiac pacemakers and arrhythmias triggered by micro re-entry. These are potentially more serious and even life-threatening.

There is considerable variation in the plasma and tissue concentrations at which toxicity occurs because of differences between patients in sensitivity and vulnerability of the myocardium, the conducting system, and other tissues. For digoxin, serious manifestations of toxicity are unusual with plasma concentrations below 2 µg/l (2.56 µmol/l) but are likely to be present with concentrations over 3 µg/l (3.84 µmol/l).³⁵ Between these figures some patients have a satisfactory therapeutic response while others show evidence of serious toxicity.

The extracardiac manifestations of digitalis toxicity were studied after a manufacturing accident in Holland³⁷; digitoxin was inadvertently substituted for digoxin and therefore administered to a community in excessive dosage. Fatigue and profound muscular weakness were almost invariable. These are very non-specific symptoms, readily ascribed to the underlying disease, the effects of inactivity, or even imagination. We now know that they deserve closer attention in patients treated with glycosides. Other symptoms in the Dutch study included the expected visual and gastrointestinal disturbances, together with headache, restlessness, and agitation. Muscular cramps have also been reported.³⁸

In the absence of myocardial disease the cardiac manifestations of high plasma concentrations of cardiac glycosides are relatively benign. Though first, second, and third degree atrioventricular blocks

occur, prolonged pauses are infrequent because the automaticity of subsidiary pacemakers is enhanced. In patients with heart disease the manifestations are more complex and more serious. The association of tachycardias with atrioventricular block is characteristic; frequent ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation are well recognised, but some digitalis arrhythmias are very difficult to characterise.

An early warning of digitalis toxicity which often passes unheeded is progressive regularisation of the ventricular response in atrial fibrillation.³⁹ The physician should make a habit of deciding whether or not the heart rate with atrial fibrillation is as "irregularly irregular" as his teachers had him believe.

Very high plasma concentrations of digitalis may be associated with severe hyperkalaemia and asystole. This cannot be treated successfully by conventional methods, though the use of specific antibody fragments will have a role in the severest forms of intoxication if such treatment becomes commercially available.⁴⁰

Some authorities consider that digitalis should be used with particular caution in patients with severe ischaemic heart disease because the threshold to ventricular fibrillation may be lowered in this group which is already at high risk from sudden death. Moss and colleagues demonstrated that patients treated with digitalis were more likely to die suddenly than others not so treated.⁴¹ Three other studies have implicated digitalis as an independent risk factor after infarction, though the Coronary Artery Surgery Study did not.⁴² Adequately controlled trials cannot readily be conducted and a misleading impression may be obtained if patients with more severe disease tend to receive treatment with glycosides. For the moment the verdict on this point must be "under suspicion but not proven".

Drug interactions

The interactions of digoxin and digitoxin with other agents have been described in over 400 papers listed in *Index Medicus* since 1980, and in very many more over the previous decade. The wise physician should hesitate before prescribing a glycoside with any other drug. This is indeed serious advice since digitalis has a perilously low therapeutic ratio.

Interactions can occur because of induced variations in absorption, or metabolism, or excretion in urine or bile; variations in protein or tissue binding, because of changes in adenosine triphosphatase activity, and because of additive or competitive effects on cardiac tissues. Many interactions involve more than one mechanism, some have not been fully elucidated, and doubtless many remain unknown.

The absorption of digoxin from the gut is incomplete and therefore variable. Agents such as propantheline that slow transit time through the bowel will increase digoxin absorption while agents such as metoclopramide that speed emptying will decrease it.⁴³ Resins such as cholestyramine⁴⁴ and even simple antacids⁴⁵ will readily adsorb digoxin and retain it within the gut lumen. Are house officers aware of this when antacids are given on demand to patients with atrial fibrillation? Digitoxin, which is usually completely absorbed, is less vulnerable, but cholestyramine and antacids also influence absorption of this glycoside.

Microsomal enzymes which are responsible in part for the hepatic metabolism of digitoxin are inducible by phenobarbitone and phenytoin. Plasma concentrations of the glycoside can therefore be reduced by these drugs.⁴⁶ Digoxin is metabolised within the gut by *Eubacterium lentum* in some individuals.¹¹ Hence, agents such as antibiotics that alter gut flora may have profound effects on the bioavailability of digoxin.

The excretion of digitoxin in bile and its enterohepatic cycle are subject to interference. Cholestyramine can bind the glycoside and prevent reabsorption. This effect can be used to counteract digitoxin toxicity, since the plasma half life can be markedly reduced with the resin.⁴⁷ The renal excretion of digoxin is partly by glomerular filtration and partly by tubular excretion.⁴⁸ The latter is susceptible to interference by triamterene and spironolactone. Increases in plasma concentrations are relatively small. Moreover, canrenoate (a metabolite of spironolactone) probably competes for myocardial binding sites⁴⁹; thus higher plasma concentrations may not be reflected by higher tissue concentration.

Drugs known to be albumin bound, such as sulphonamides, phenobarbitone, and tolbutamide, displace digitoxin and change the ratio of free to bound drug within the plasma. But the effects are small and of only minor clinical importance.⁴⁶

The mechanisms of some important interactions are not completely understood, partly because they are complex. Quinidine, for example, may influence absorption, excretion, and apparent volume of distribution of digoxin.⁵⁰ Plasma concentrations are increased but displacement from myocardial receptors has been postulated. Verapamil,⁵¹ amiodarone,⁵² nifedipine,⁵³ and ibuprofen⁵⁴ are also among common drugs that increase plasma digoxin concentrations. Symptoms arising within the central nervous system are exacerbated, but serious toxicity may depend more on whether tissue concentrations are increased or decreased; evidence on this point is sparse. Rifampicin decreases plasma concentrations of glycosides, especially of digitoxin.⁵⁵

The plasma potassium concentration influences digitalis effects by affecting sodium-potassium adenosine triphosphatase.⁵⁶ Most clinicians recognise the peril of hypokalaemia from diuretics used in heart failure, which is usually exacerbated by high aldosterone levels. Less well recognised is the rapid and often profound hypokalaemia mediated by beta₂ receptors as a result of intense sympathetic stimulation.⁵⁷ How far the danger of this is exacerbated by concomitant treatment with glycosides and how far treatment with non-selective beta blockers can be protective remain speculative.

Competing or additive inotropic and chronotropic effects from other cardioactive drugs merit little comment. The concept of an inotropic ceiling may be worthy of mention, however. This refers to the inotropic reserve that exists even in the failing heart. It is not clear whether the ceiling of augmentation can be reached by inotropic drugs,⁵⁸ but additive effects are unlikely. Thus there may be little point in using digitalis for acute heart failure if more powerful agents such as catecholamines are given concurrently. Cardiac glycosides may have a role, however, during the difficult withdrawal of catecholamines when there is down regulation⁵⁹ of beta receptors.

Digitalis: where are we now?

The cardiac glycosides are difficult and dangerous drugs and they are used in vulnerable patients. We would abandon them if we had effective substitutes. The introduction of better diuretics, vasodilators, and perhaps alternative oral inotropic agents⁶⁰ has reduced the role of digitalis for the long term management of heart failure but we still require the agent that Withering gave us 200 years ago. We need it for the control of atrial fibrillation in many patients, for treatment and prophylaxis of supraventricular tachycardias in a few, for acute left ventricular failure in most, and for chronic heart failure when other options seem inadequate. Perhaps digitoxin with its more predictable absorption and elimination and more constant plasma concentrations deserves more emphasis, and perhaps the rapid action of ouabain is insufficiently exploited.

Digitalis in its varying forms still has an important role and we cannot do without it. But each time a glycoside is prescribed the clinician should ask whether it is worth the risk of unwanted effects, will it suit the need better than other drugs, and how closely should the patient be supervised. We must not use digitalis needlessly nor unthinkingly. Where are we now? With the benefit of our new knowledge we are in a better position than ever before to use digitalis with the assurance that benefit should outweigh harm. Let those who have not done so take

time to read Withering's treatise which still has much useful advice to offer.

The use of the Foxglove is getting abroad, and it is better that the world should derive some instruction, however imperfect, from my experience than that the lives of men should be hazarded by its unguarded exhibition or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.¹

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Drug treatment of heart failure*

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In his classic *Account of the Foxglove*, William Withering gave a vivid description of patients with terminal heart failure and meticulous case reports of their dramatic diuresis in response to digitalis.¹ Though Withering remarked on the action of digitalis upon the heart he regarded it primarily as a diuretic and did not make the connection between its diuretic and cardiac action. Withering was well aware of the hazards of digitalis overdose but despite his warnings it was widely prescribed in high doses for oedema of non-cardiac origin and for a wide variety of other conditions. Its lack of effect in many of these cases and its pronounced toxicity caused it to fall into disrepute.

In the nineteenth century polypharmacy was in fashion and digitalis was used, if at all, in combination with other agents such as mercury and squill (Baillie's pills; Guy's Hospital pills).² Even early this century the merits and dangers of coffee, strychnine, camphor, and cane sugar in heart failure aroused hot debate.³⁻⁵ Purgation, cupping, vesication and sweating were widely practised.⁶ The removal of excess fluid was known to produce pronounced clinical improvement and if treatment with digitalis and purgation failed then mechanical means were used.⁷ In the last resort Southey's tubes were used to drain the extracellular fluid, with all their attendant discomfort, scarring, and risk of cellulitis.⁸ Heart failure is an unpleasant illness but the misery inflicted by inappropriate, toxic, or dangerous treatment must often have been greater than that of the disease itself.

Certainly some early treatments, especially venesection, were capable of bringing short term benefits in heart failure. Bloodletting was said to "afford more speedy and compleat relief than any other remedy".⁹ But physicians lacked understanding both of the diagnosis and the pathophysiology so that they used different methods without discrimination. Modern physiology established a more rational basis

for treatment. Howarth *et al* demonstrated haemodynamic improvement after venesection in patients with congestive heart failure who had a very high venous pressure. The cardiac output rose as the venous pressure fell.¹⁰ The importance of salt and water excess in oedema formation was clarified by Starling in his classic experiments when he perfused isolated animal limbs.¹¹ In consequence strict and unpalatable dietary restriction of salt and water was advocated.¹²⁻¹⁴

It was not until Vogl in 1920 reported the diuretic effect of the organomercurial merbaphenum, then a treatment for syphilis, that the era of effective diuretics began.¹⁵ Mersalyl, a direct development from merbaphenum, was the first effective means of treating oedema.^{16,17} Organomercurial diuretics could produce haemodynamic improvement with a rise in cardiac output and a fall in right atrial pressure.¹⁸⁻²⁰ Unfortunately they had to be administered parenterally and were toxic. Local tissue necrosis followed a badly placed injection and chronic administration produced manifestations of mercurialism which varied from stomatitis to the nephrotic syndrome.²¹⁻²⁵ Hypersensitivity reactions although uncommon were occasionally fatal.^{26,27}

The search for an orally effective diuretic continued, but most of those produced were relatively ineffective.²⁸⁻³¹ Just as astute clinical observations during the use of merbaphenum in syphilis led to the development of mersalyl, so clinical observations of a diuresis during treatment with antibacterial sulphonamides were to lead eventually to the discovery of the benzothiadiazine diuretics. The synthesis of chlorothiazide by Novello and Sprague in 1957³² was the most important single advance in the symptomatic relief of heart failure. Although less potent than the organomercurials,³³ the thiazides were effective orally even in those patients who had become resistant to mercurial diuretics and they were also much less toxic.^{34,35} They were not, however, without their problems. One of their major side effects was hypokalaemia which could be profound,³⁶ inducing hepatic coma in patients with cirrhosis³⁷ and sensitising the myocardium to the toxic effects of digitalis in patients with congestive cardiac failure.³⁸⁻⁴⁰ None the less, they remain an

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*The William Withering Lecture of the Royal College of Physicians, 1985

important tool in the management of heart failure.

Diuretic resistance remained common until the era of the so called "loop" diuretics frusemide and ethacrynic acid. These are both extremely potent and quite well tolerated.⁴¹⁻⁴⁴ Their efficacy, even in those patients who no longer respond to thiazides, means that the diuretic resistant patient is now rare.⁴⁵

The salt retaining corticosteroid, aldosterone, was identified⁴⁶ at almost the same time as the discovery of the oral diuretics. For many years it was believed that secondary hyperaldosteronism was mainly responsible for the salt and water retention in congestive heart failure and much research was concentrated on this mechanism. Spironolactone (a specific aldosterone antagonist), however, proved to be relatively ineffective in cardiac oedema. The position was finally clarified in 1974 by Nicholls *et al* who showed that aldosterone concentrations were slightly raised in untreated heart failure and fell to normal as body weight declined during diuretic therapy.⁴⁷ It was only as the body weight stabilised and the patient became salt depleted that the aldosterone levels rose sharply to 4-6 times normal. Knight *et al* demonstrated a highly significant correlation between the dose of frusemide and the plasma aldosterone concentration.⁴⁸

Release of renin from the kidney is critical and there appears to be a two stage mechanism. In heart failure renal blood flow is slightly reduced and an increase in renin release follows. Circulating angiotensin II stimulates aldosterone secretion from the adrenal and plasma aldosterone becomes slightly raised. As patients become salt depleted and "dried out" there is a secondary and much greater rise in renin and aldosterone.⁴⁷

Modern diuretics have transformed the symptomatic treatment of a patient with dropsy and would have greatly impressed a physician of Withering's era. But they are only part of the story and are not without their problems. The patient who has been dried out with diuretics may look better but the other problems of heart failure remain—fatigue, limited exercise capacity, cachexia, and salt depletion with a high plasma aldosterone and renin. A fully effective treatment for heart failure should restore exercise capacity and improve life expectancy as well as relieve symptoms.

Exercise capacity

With the advent of invasive haemodynamic monitoring,⁴⁹⁻⁵¹ the effect of drug treatment on different aspects of the failing circulation became clearer.^{52,53} Unfortunately, most studies were performed in the catheter laboratory and the obser-

vations lasted at most a few hours. They yielded valuable information on the control of the cardiovascular system but were a poor guide to long term therapeutic responses.⁵⁴ Haemodynamic indices such as cardiac output correlate very poorly with exercise duration and capacity in patients with heart failure.^{55,56} More sophisticated haemodynamic indices, even those determined during exercise testing also fail to show any significant correlation with exercise capacity.⁵⁷⁻⁵⁹

Attempts to improve exercise capacity in heart failure must take into account normal circulatory control during exertion. Cardiac output at rest is normally about 5-6 litres of which about half goes to the splanchnic and renal beds and a quarter to skeletal muscle. Under conditions of maximal exercise there is an enormous increase in cardiac output (for example to 24 litres) primarily to skeletal muscle.⁶⁰ In addition a rationing system is introduced which curtails the flow to inactive muscle and the splanchnic and renal beds while allowing the coronary flow to rise and the cerebral blood flow to remain virtually unchanged. Mason *et al* have demonstrated that the rationing system imposed on the normal circulation during exercise is active in heart failure patients at rest.⁶¹ The total cardiac output at rest is generally lower with more going to skeletal muscle and less to the renal and splanchnic beds. During exercise, this imbalance becomes even more pronounced.

There is one further adaptation of the circulation in heart failure. Franciosa showed that for a given workload the oxygen consumption of a group of patients with congestive cardiac failure of varying severity is virtually identical to that of a group of normal controls.⁶² At each workload, however, the cardiac index of the patients with congestive cardiac failure was lower than in the controls, indicating increased extraction of oxygen from the capillary blood. The main difference between controls and those with heart failure of different degrees of severity was the load/duration at which they had to stop.

An objective measure of maximal exercise capacity, such as the maximal oxygen uptake, is desirable for the comparison of different drugs used in the treatment of heart failure. Maximal oxygen uptake is a sensitive test for differentiating the severity of heart failure.⁶² Unfortunately in most of the protocols used for testing exercise capacity in patients with congestive cardiac failure the workload is doubled every few minutes.⁶³⁻⁶⁵ Such protocols may be appropriate for threshold testing in patients with angina, but they have the effect of telescoping the variation in duration of exercise at higher workloads in patients with congestive cardiac failure and of reducing the sensitivity of the method for detecting benefit. A fixed workload, if necessary one calculated

individually for each subject, would be more appropriate.

CRITERIA FOR ACCEPTABLE STUDIES

In our review of the vast number of published reports on the drug treatment of congestive heart failure we have concentrated on studies which were double blind, included a placebo control, and assessed the effect of treatment upon exercise capacity. We have included only those studies which assessed longer term effects of drug therapy on exercise capacity, since these have been shown to differ from short term effects.⁶⁶ Unfortunately we have therefore had to exclude many papers. Ideally we should have applied two further exclusion criteria—firstly that the numbers of patients studied were sufficiently large to have confidence in the significance of a negative result, that is to say that the study included a calculation of statistical power as well as significance; and secondly that the results were analysed on an intention to treat basis rather than on the basis of the patients who completed the protocol. Had we applied these additional criteria too few papers would have been left for conclusions to be drawn.

Two broad categories of drugs have been used to try to increase exercise capacity in patients with heart failure; these are vasodilators and positive inotropic agents.

VASODILATOR THERAPY

Vasodilators were introduced into the treatment of heart failure as a result of haemodynamic research and with the aim of reducing preload and afterload.^{67,68} They have profound immediate haemodynamic effects and were hailed by many as the most important advance in treatment since digitalis and the diuretics. Despite the improved haemodynamics associated with their use, short term studies did not always show an increase in exercise capacity.⁶⁹ Moreover, the effect of long term treatment on exercise capacity was neglected until the past decade.

A wide spectrum of vasodilator drugs is currently in use, the most common groups being direct acting venodilators (such as nitrates), arteriolar dilators (such as hydralazine), α_1 adrenoceptor blocking drugs (for example prazosin, trimazosin), and the angiotensin converting enzyme inhibitors (captopril, enalapril). The β_2 receptor agonists, such as salbutamol, are now thought to be too arrhythmogenic for widespread use.

In a randomised double blind placebo controlled study of 32 patients followed up over 26 weeks, Franciosa *et al* found a significant improvement in exercise duration on hydralazine over the first four weeks (mean (SEM) 259(21) to 347(35) s, $p < 0.01$)

and a further rise at 26 weeks (421(38) s, $p < 0.001$).⁷⁰ Exercise duration, however, also increased significantly in the placebo group over the first four weeks (271(30) to 340(44) s, $p < 0.02$) and at 26 weeks (339(46) s, $p < 0.02$). There were no significant differences between the two groups at any time during the study and this evidence emphasises the need for adequate placebo controls. In a further study with hydralazine by Conradson *et al*, the difference between the treated and control group just reached statistical significance at six months ($p < 0.05$) but this advantage was lost by 12 months ($p = 0.14$).⁷¹ Only half of the patients who entered the study completed it; most dropped out because of worsening heart failure. If the results had been analysed on an intention to treat rather than the on treatment basis it is unlikely that there would have been a significant difference between the two groups.

Similar results were reported by Leier *et al* with isosorbide dinitrate in a study of 30 patients over 12 weeks.⁷² Both the treated and the control groups showed a small increase in their exercise duration, with the difference just reaching statistical significance at 90 days. A similar trend was seen with prazosin over six months' treatment (mean (SD)) (541(204) to 630(100) s) compared with placebo (531(141) to 435(148) s), but the difference between the groups was not significant.⁷³ Other studies with prazosin and trimazosin have shown a small improvement in the treated group over baseline values which was not seen in the placebo group but in most cases the difference in improvement between the groups was not significant.⁷⁴⁻⁷⁶

Whether or not the improvement on vasodilators was just significant, the disappointing fact remains that the degree of improvement so far demonstrated with vasodilators is not of sufficient magnitude to make a substantial difference to the patient's life. It is debatable whether the improvement in most of the trials would be of any real clinical value.

The last category of drugs included, somewhat loosely, under the heading of vasodilators is the angiotensin converting enzyme inhibitors. Here the results are somewhat more encouraging. Cleland *et al* found a highly significant increase in exercise time from 336(228) to 546(318) s (mean(SD)) ($p < 0.005$) in 14 patients after 12 weeks' therapy with captopril. With placebo substitution, exercise time fell to 456(258) s ($p < 0.03$).⁷⁷ A less pronounced improvement was seen in a similar study by Cowley *et al* (mean (SEM)) (726(77.4) to 894(70.2) s, $p < 0.05$) but they studied patients with milder heart failure over a shorter period of four weeks.⁷⁸ A much larger multicentre study with 92 patients over 12 weeks showed a 24% increase in exercise tolerance (495(22) to 614(27) s) with captopril as compared

with a 0.4% increase with placebo (mean (SEM)) (480(28) to 483(43) s, $p < 0.01$).⁷⁹ Furthermore the difference between the two groups became more pronounced as the study continued, and the exercise tolerance of the treated group was still rising at 12 weeks. The largest study of an angiotensin converting enzyme inhibitor was an international multicentre study of enalapril in 256 patients. Again the treated group had significantly better exercise tolerance than the placebo group at 12 weeks and the difference continued to increase up to 24 weeks ($p < 0.001$).

Angiotensin converting enzyme inhibitors may be the only group of "vasodilators" which offer a real advantage for patients in heart failure. Besides their effect upon peripheral vascular resistance they also reduce aldosterone secretion and have a mild diuretic action in contrast to the salt retaining action of all other vasodilators.

INOTROPES

For almost 200 years the mainstay of treatment for congestive heart failure has been inotropic therapy with digoxin. With reservations about the dangers of increased myocardial oxygen demand, the use of drugs with a positive inotropic action to increase the low cardiac output of heart failure appears the most promising therapeutic approach. Powerful inotropes such as isoprenaline increase the resting cardiac index⁸⁰ but their value in the management of patients with chronic congestive cardiac failure is not established. Despite its long history, controlled trials of digoxin treatment in patients with congestive heart failure who are in sinus rhythm were not done until the value of such treatment began to be questioned about 10 years ago. Since then scepticism has grown after several studies in which either no benefit could be demonstrated or, if present, was very small.⁸¹⁻⁸³ Some studies such as those by Lee *et al*⁸⁴ and Arnold *et al*⁸⁵ have shown clinical or haemodynamic benefit, but maximal exercise capacity was not improved in a non-randomised, double blind, placebo controlled withdrawal study of 12 patients by Fleg *et al*.⁸⁶ According to the criteria we have adopted, a benefit of digitalis in patients with heart failure treated with diuretics has not been established.

Most of the more powerful inotropic agents approved for clinical use have to be given intravenously and thus cannot be used routinely in long term outpatient management of congestive heart failure. To overcome this disadvantage several orally active positive inotropes, such as the bipyridine derivatives amrinone and milrinone, have been developed and have generated intense interest.⁸⁷ Amrinone showed some initial promise when Weber *et al* reported a

sustained increase in maximal oxygen consumption in patients taking the drug orally for 12 weeks.⁸⁸ But a lack of improvement seen in small studies⁸⁹ has been confirmed by the findings of a much larger multicentre study of 173 patients.⁹⁰ The 52 patients who showed the best response to the drug in the open phase were randomised in a double blind fashion to either continue amrinone or to receive placebo. Subsequent comparison of the two groups showed similar falls in exercise time (7% and 10% respectively) and no significant difference between them. The lack of long term efficacy coupled with a high incidence of adverse reactions has prompted the withdrawal of amrinone from clinical trials except as acute intravenous therapy. We await the results of trials with its congener, milrinone.

Unexpected encouragement to continue the search for better inotropic agents has come from studies of the intravenous administration of dobutamine. Liang *et al* studied 15 patients with congestive cardiomyopathy who were given 72 hour infusions of dobutamine or placebo in a randomised double blind placebo controlled trial which included measurement of exercise capacity over four weeks.⁹¹ There was a significant difference in treadmill exercise time between the two groups which was sustained over four weeks ($p < 0.05$). Though it is difficult to postulate a mechanism for this long duration of action, some support for the findings comes from a previous uncontrolled study of intermittent shorter infusions given to outpatients weekly for 24 weeks.⁹² Dobutamine looks reasonably promising but we must await the outcome of larger controlled trials before the benefits and the effects of mortality and morbidity can be assessed.

Overall the effects of vasodilators and positive inotropic agents in heart failure are unimpressive when measured against the extent of the patient's disability. The degree of benefit, however, that can be attained must ultimately be limited by the severity and reversibility of the damage to the heart muscle.

Prolongation of life

An effective treatment of heart failure ought to prolong life as well as provide symptomatic relief. It is instructive to examine the evidence that any form of treatment can improve survival.

PROGNOSIS OF HEART FAILURE

The prognosis of congestive heart failure is as grave as that of many malignant neoplasms. In the Framingham study overt evidence of congestive heart failure developed in 142 of the original cohort of 5192 over 16 years.⁹³ Despite medical management the probability of dying within five years from the onset

of heart failure was 62% for men and 42% for women. Mortality rates of about 35% at one year were found in several smaller studies by Massie *et al.*,⁹⁴ Franciosa *et al.*,⁹⁵ and Unverferth *et al.*⁹⁶ The cumulative mortality of medically refractory heart failure is even worse—42% at one year and 68% at two years.⁹⁷

Patients with heart failure do not all die from a progressively falling cardiac output; sudden death is also important. Wilson *et al.*, who defined a death as sudden if the patient was known to have been clinically unchanged in the previous week and stable one hour before death, reported that approximately 50% of deaths were sudden and that the rest were due to progressive heart failure.⁹⁷ Other estimates of mortality attributable to sudden death vary from 11% to 60–90%.^{98–100}

It is interesting that the Beta-blocker Heart Attack Trial showed a reduction in the relative mortality rate for patients with mechanical as well as electrical complications of acute myocardial infarction who were treated with propranolol.¹⁰¹ Prevention of sudden death from arrhythmias may provide a means of improving survival in patients with congestive heart failure.

No properly designed studies have been carried out to investigate the effects of vasodilators or positive inotropic agents upon mortality. Pooling the published controlled studies suggests that mortality with most drugs (for example, alpha blockade, hydralazine, isosorbide) is either unchanged or increased. The combined data from the much larger trials with the angiotensin converting enzyme inhibitors captopril and enalapril are more encouraging. The effect of the angiotensin converting enzyme inhibitors on mortality in heart failure should now be investigated in a large properly designed trial.

Tunstall Pedoe studied changes in national mortality statistics over two periods when the bioavailability of digoxin was changed.¹⁰² There was little change in the dose of digoxin prescribed over these periods and no consistent change in mortality. This implies that the increased bioavailability of digoxin itself was not an important cause of mortality, but neither was it beneficial.

PREVENTION OF HEART FAILURE

There is evidence that some deaths from heart failure may be preventable. The Medical Research Council Home Oxygen Trial showed that 19 of the 42 patients with chronic hypoxic cor pulmonale who were treated with long term oxygen therapy died in the five years of survival follow up compared with 30 of the 45 controls.¹⁰³ In the Veterans Administration Study of cor pulmonale 88% of the responders to

home oxygen (that is those who had a fall in their mean pulmonary arterial pressure) but only 22% of the non-responders were alive at the end of two years.¹⁰⁴ These trials, however, involved patients taking oxygen at home for at least 15 hours a day and the quality of the life that was prolonged must have been much restricted.

There is one further area where preventive treatment seems to have led to a major reduction in mortality from cardiac failure. This is the treatment of hypertension. Several therapeutic trials in patients with severe hypertension^{105–107} showed that adequate control of blood pressure prevents the development of heart failure. It is noteworthy that in the Framingham study hypertension preceded the development of heart failure in 75% of cases.⁹³ Further evidence is provided by a review of the mortality data for England and Wales from the Registrar General's annual reports under code 402 (deaths from hypertensive heart disease). While there must be some reservations about the possible alternative coding in another category of deaths from this cause, the

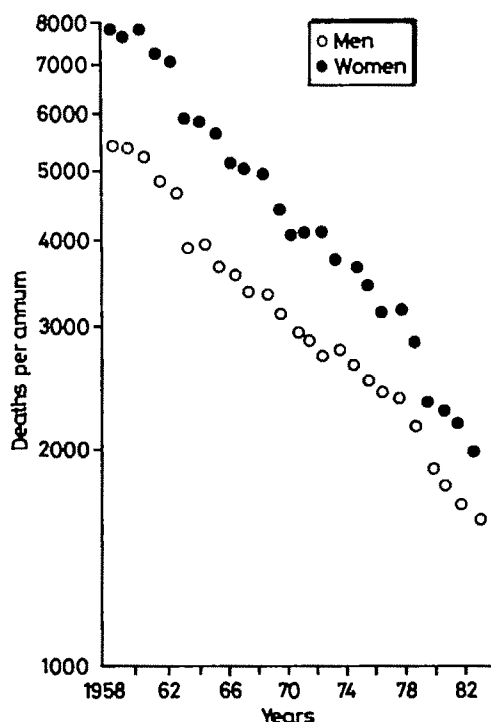


Fig. Mortality from hypertensive heart disease in England and Wales since 1958. (Source: Code 402 from the Registrar General's annual reports.)

figures show a 75% fall in mortality from hypertensive heart disease since 1958 and deaths in those with hypertensive heart disease are probably mainly caused by heart failure (see Fig.).

Future prospects

Despite the success of diuretics, it is a sobering thought that other advances in therapeutics over the last 200 years such as the discovery of penicillin and the treatment of tuberculosis would impress a physician of Withering's era far more than our use of vasodilators and inotropes for chronic heart failure. Indeed Withering himself, a forward thinking member of the Lunar Society, would probably be dismayed to find that we are still using digitalis, a drug which he recognised to be highly toxic and of limited efficacy. Perhaps only the angiotensin converting enzyme inhibitors and the modern management of hypertension would provide him with some faith in our progress in the treatment of heart failure.

The best hope for the future is probably to concentrate on preventive measures such as reduction in cigarette smoking, treatment of hypertension, myocardial salvage during infarction, and even the prevention of atheroma. There may also be some scope to improve active treatment by combining inotropes with angiotensin converting enzyme inhibitors and perhaps by combining the inotropic action of a drug like dobutamine with the antiarrhythmic action of propranolol in a molecule which is a partial beta₁ receptor agonist. Heart failure will have to be treated less as a global end stage disease and more as the specific outcome of diseases such as ischaemic heart disease and cardiomyopathy. Continued advances in treatment are much needed.

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Changing digoxin potency and cardiac mortality in England and Wales 1968-76

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SUMMARY Data on monthly totals of cardiac deaths in England and Wales were examined in different ways to see whether there were any unexplained fluctuations in rates both at the time of an unplanned increase in the bioavailability and therefore the potency of the Lanoxin brand of digoxin in May 1972 and also when there was a coordinated increase in the bioavailability of other brands in October 1975. Despite advice to prescribers, dosages were not proportionately reduced in the 600 000 patients who were on treatment. Monthly totals of deaths from cardiac causes were high through the summer of 1972 but not at the end of 1975 and the excess in 1972 seems to be related to a cold summer. There was no evidence of a consistent or specific effect of changes in digoxin potency, either beneficial or harmful, on deaths from all cardiac causes or in specific subgroups in which digoxin treatment was likely to be most common. Although major changes in digoxin potency in England and Wales did not seem to produce a repeatable effect on death rates, data from other countries should also be examined for evidence of such an effect.

Digitalis is an old established drug widely used in the form of digoxin for the control of atrial fibrillation and the treatment of congestive cardiac failure.^{1,2} Its therapeutic index, however, is low, individual dosage is variable, particularly in the elderly in whom it is often prescribed, and toxic effects such as anorexia and rhythm disturbances may be confused with the conditions it is used to treat. Its value in improving symptoms is accepted but it is not known whether its mass usage in the population is beneficial or harmful since it has never been the subject of a large scale controlled trial such as is used for new drugs; however, some small scale trials have been reported.^{3,4} But digoxin has been the subject of two natural experiments in the United Kingdom. In 1969 the potency of the leading proprietary brand, Lanoxin, was reduced by about half as a result of a change in manufacturing procedures which affected its bioavailability. This was followed in the summer of 1972 by an unplanned doubling of potency at a time when new tests of bioavailability were being intro-

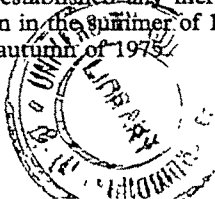
duced. Consequently a new standard for bioavailability was set, and there was a planned synchronised increase in the potency of all other brands in October 1975.

A previous study explored what happened to dosage levels and prescribing habits over this period.⁵ An estimated 600 000 patients were found to be on long term treatment including 6% of the population over 65. Although mean daily dosages showed a steady decline in the period 1967-76, there was no sudden change in dosage at the time of the changes in digoxin potency. In contrast to the small scale controlled trials, the natural experiment therefore involved a study population of 600 000 who underwent a sudden increase in the effective dosage in 1972 and 1975.

Because digoxin is used exclusively for heart disease most of those who died from toxicity or whose lives might have been prolonged by the increased effective dosage would probably have had a diagnosis of heart disease shown on the death certificate. I therefore decided to examine the monthly trends in deaths for England and Wales attributed to heart disease over several years with an *a priori* requirement that if an association with changes of digoxin potency was to be established any increase or decrease in deaths seen in the summer of 1972 should also be seen in the autumn of 1975.

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Accepted for publication 26 April 1985



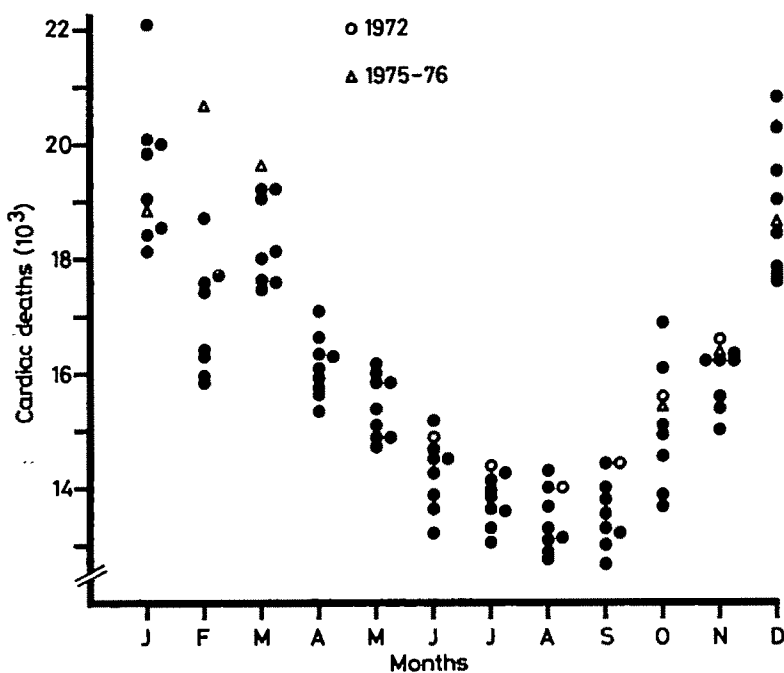


Fig. 1 Monthly totals of cardiac deaths 1968-76 showing how the six months from May 1972 and October 1975 compare with corresponding months in other years.

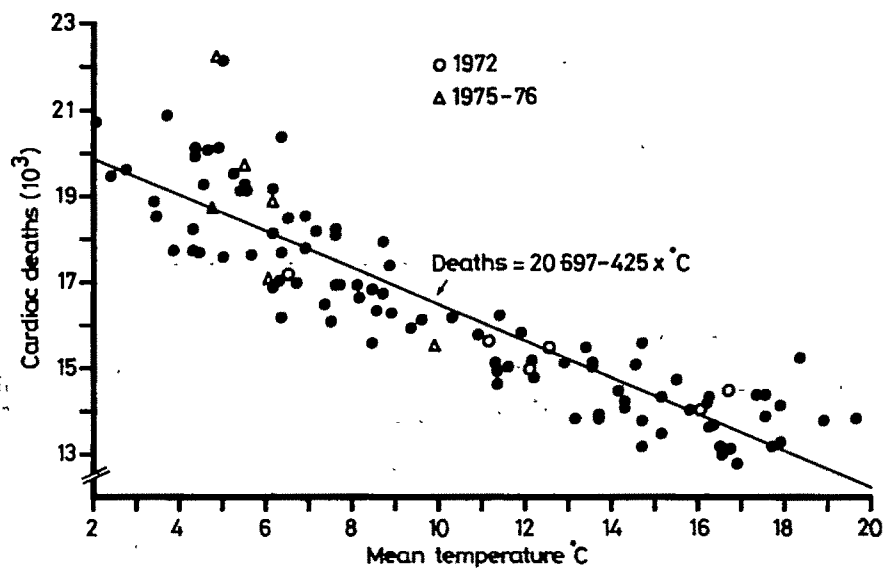


Fig. 2 Monthly totals of cardiac deaths 1968-76 corrected to 31 days and plotted against mean monthly temperature recorded at Kew.

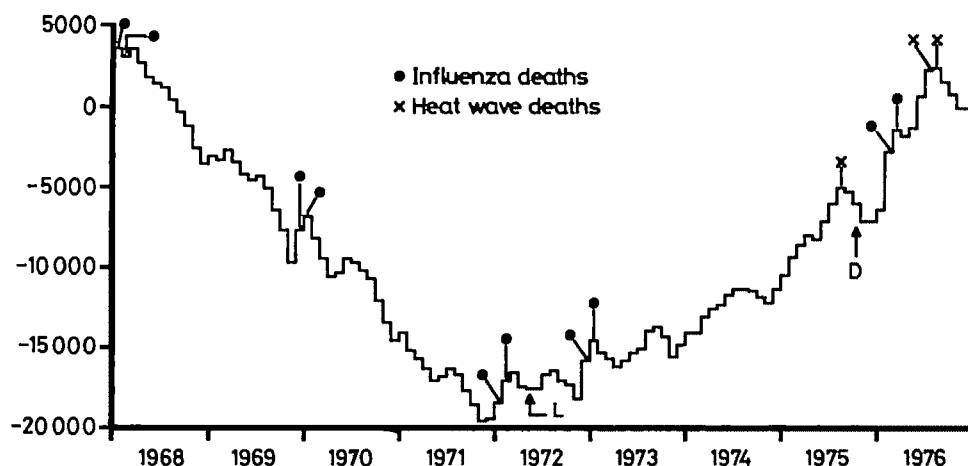


Fig. 3 Cumulative sum graph of observed minus expected cardiac deaths per month 1968–76 corrected for temperatures to show changes in trends. Months marked are those when influenza deaths exceeded 200 or when the mean temperature was above 18°C. L, change in potency of Lanoxin brand of digoxin; D, general change in digoxin potency.

Patients and methods

Monthly totals of deaths in England and Wales were extracted from the Registrar General's publications from the years 1968 (when a new disease classification was introduced) to 1976.⁶ Different categories of deaths were looked at including deaths from all causes, respiratory deaths (International Classification of Disease rubrics 460–519), neoplasms (140–239), cardiovascular deaths (390–458), cardiac deaths (390–429), and different subgroups of the latter.

Cardiac deaths were subjected to special analyses. Because of the excess of deaths in the winter months, often accompanied by influenza epidemics and also related to the ambient temperature, the monthly totals for each year were displayed graphically, picking out the six months after the increase in Lanoxin potency in May 1972 and the increase in potency of other digoxin brands in October 1975 (Fig. 1). The number of deaths in each month was then adjusted upwards if necessary to correct for the shortfall from 31 days and they were plotted against the mean monthly temperature at Kew (Fig. 2).

A third technique was then used to explore these data in a different way. A regression equation was calculated to fit the data in Fig. 2 to relate numbers of cardiac deaths per month to the mean monthly temperature (corrected monthly death total = 20 697 – 425 × the mean monthly temperature in degrees C). For each month from the beginning of 1968 the formula was used to calculate sequentially

the expected number of deaths and any discrepancy (positive or negative) between that and the observed number was found. These were then put together by means of the cumulative sum (CUSUM) technique in which the discrepancies are added serially and plotted, so that a change in the gradient of the line shows that a new factor is operating (Fig. 3).⁷

Finally, I analysed the numbers of deaths per month in different cause groups. Periods of four months' duration after the two increases in potency were compared with the four month periods preceding the increase. Each monthly total in each category for February 1972 to May 1972 and for June 1975 to September 1975 was divided by the average number of deaths in that disease category in that calendar month during the years 1968 and 1976 to obtain a monthly score (this time uncorrected for temperature). The same calculation was done for the two four month periods June to September 1972 and October 1975 to January 1976. The sum of the scores for the eight post-potency increase months was then divided by the sum of the scores for the eight pre-potency increase months to obtain a ratio (Table).

Results

A scatter diagram of number of cardiac deaths in each calendar month over the nine years is shown in Fig. 1. The results for June, July, August, and September 1972 are all rather high, there is no excess in October, but there is a rather high reading in November. The figures for October 1975 are average,

Table Ratio of post-potency increase monthly scores to pre-potency increase monthly scores

Cause of death (ICD)	Number of deaths in May 1972	Post-potency to pre-potency ratio of deaths
All causes	46834	0.97
Neoplasms (140-239)	10121	0.98
Respiratory (460-519)	5513	0.92
Cardiovascular (390-458)	24573	0.99
Cardiac (390-429)	15833	1.01
Rheumatic heart (393-8)	534	0.96
Mitral valve (394)	237	0.95
Symptomatic heart (427)	1076	0.98

those for November are high, while those for December and January 1976 are below average; an influenza epidemic increased the numbers for the following February and March.

Figure 2, in which monthly rates are plotted against temperatures, shows the known association. Aberrant high peaks at the lower temperatures were related to influenza epidemics, and those at high temperatures to heat waves. The high monthly numbers in the summer of 1972 appear to be largely explained by the temperature. Nineteen seventy two had the coldest May, coldest June, an average July, the second coldest August, and the coldest September in the nine year period, based on the mean monthly figure recorded at Kew.

The cumulated sum graph (Fig. 3) which indicates trends after correction of data for temperature shows a tendency for deaths to decline in the late 1960s, an accelerating decline at the end of 1970 through 1971, and a change of trend at the beginning of 1972. Lanoxin potency was changed in May 1972 during a level phase and a positive gradient appears to start in late 1972. In contrast there was no obvious change in trends with the planned increase in potency of other digoxin brands in October 1975, which occurred during a period of five months when rates were lower than expected and was followed by an erratic year in 1976 when there was an influenza epidemic followed by summer heat waves. Both of these factors were associated with an excess of deaths in patients with heart disease.

The ratio of post-potency increase monthly scores to pre-increase scores (Table) shows no effect that seems to be specific to digoxin. Although the ratio for all cardiac deaths increased more than the ratios for deaths from all causes and for cardiovascular, respiratory, and neoplastic deaths, if this increase were the effect of a change in digoxin therapy there should have been an exacerbation in the categories of heart disease in which digoxin is most commonly used such as rheumatic heart disease, mitral heart disease, and the symptomatic heart disease category (which includes those patients in whom heart failure and

arrhythmias were diagnosed without an underlying specific abnormality).

Discussion

Use of national mortality figures to determine the effects of medication is an unusual technique but has an important precedent. Asthma deaths were shown to rise in young people at a time when new pressurised aerosols that dramatically relieved symptoms were being widely introduced.⁸ Cardiac disease treated by digoxin is chronic and usually managed in the community and patients usually die while they are on this medication. An increase (or decrease) in such deaths would not be detected by an individual clinician or clinic unless the change was considerable. This is because a limited number of patients are treated in any one centre, sporadic fluctuations in deaths are normal, and there is not usually any formal surveillance of death rates. National mortality figures cover the pooled experience of all the patients and clinicians in the population with no loss to follow up. In this case 600 000 patients were believed to be on treatment⁵ with a mean daily dose (all ages) of about 380 µg in 1972 and of 320 µg in 1975. If 1% of these patients had died or had had their death delayed as a result of the change in potency of the drug then the death rate would change by 6000, but the chance of it coming to clinical attention in any single centre is very small.

There are several difficulties associated with the use of trends in cardiac deaths or indeed deaths from any cause. Over several years there are trends in numbers of deaths which are related to long term trends in disease rates (such as the decline in rheumatic heart disease) or to changes in the age structure of the population or to fashions in diagnosis. While such long term trends should not affect short term fluctuations, the latter are quite considerable. Rates are particularly likely to fluctuate in the winter when they are affected by the temperature, which can be allowed for (as demonstrated above), and by influenza outbreaks, which cannot since different outbreaks have different virulence and may or may not differentially affect elderly patients with heart disease. It is difficult in retrospect to prove that any fluctuation is caused by medication because death certificates do not record medication and there is no routine surveillance of the mortality of all patients who are on established drugs. If there is a fluctuation in the death rate amounting to only a few per cent it is not possible to identify which specific deaths were expected and which were exceptional without a very laborious and possibly inaccurate survey.

The excess of cardiac deaths in the summer of 1972 was unusual in that it occurred at a time of the

year when death rates are usually stable, and a link with the change in Lanoxin potency must be suspected. There are several reasons, however, for thinking that this was unlikely. Firstly, the excess seems to be largely explained by the cold summer (Fig. 2) and, secondly, there was no corresponding increase in cardiac deaths after digoxin potency had increased in October 1975. In 1972 the manufacturer realised some time after stocks were first released to suppliers that potency had changed, but the new formulation would not have reached all patients at the same time, so that there would have been a delayed and progressive impact on patients as old stocks were used up and new ones were introduced. During this time, pharmacists were being encouraged to dispense other brands against general practitioner prescriptions for Lanoxin. Thus though we know what was being prescribed⁵ we do not know exactly what was being dispensed and when. The situation in October 1975 was much more straightforward. For the non-Lanoxin brands, the high potency variant was not released before October 1975 but was dispensed exclusively after that date so that the impact on the patient population would have been simultaneous. Unfortunately the proportion of patients on medication being supplied with non-Lanoxin brands at this time is not known since many pharmacists dispensed Lanoxin against a generic prescription for digoxin and although it is claimed that Lanoxin had the bulk of the market in 1972, it was less popular afterwards and then began to recover its former position. The *a priori* hypothesis of this investigation was that any effect of a change in digoxin potency would have been repetitive, but there is no evidence that the change of potency did have a consistent effect on cardiac deaths.

Two other features argue against the claim that digoxin was responsible for any of the excess of cardiac deaths in 1972. One is that while there was a peak in the broad category of cardiac deaths, this excess was less apparent in deaths attributed to rheumatic heart disease (and specifically mitral valve disease), for which a high proportion of patients would have been receiving large enough doses to control atrial fibrillation, and also in deaths from symptomatic heart disease which tend to occur in elderly patients being treated for congestive cardiac failure. Finally there was no clinical evidence of an epidemic of digitalis toxicity at this time. This contrasts with a report from Israel where a change in digoxin potency resulted in large numbers of patients being admitted to hospital with toxic effects.⁹ Although the major changes in Lanoxin potency in 1969 and 1972 were largely unremarked and led to little change in prescribing habits by clinicians,⁵ it would be surprising if an increase in deaths from digoxin toxicity

in England and Wales could occur without prompting any comments from hospital doctors on the increase in morbidity, especially since such observations were being reported in other countries.

These observations do not establish the case for an overall beneficial or harmful effect resulting from a change in digoxin potency neither do they prove that changes in digoxin potency have no effect at all on mortality. It is possible that the increase in potency benefited some patients and harmed others and that the effects cancelled out. Several other countries introduced new standards for digoxin bioavailability at about the same time (1975). It would be useful to examine data from those countries for which monthly figures for cardiac deaths are available (as they are in England and Wales) and where the brands of digoxin which were widely available before the change were of low bioavailability. Data from any one country are likely to be affected by the extraneous factors already discussed while examination of those from several might uncover any small beneficial or harmful effect concealed in the present figures. Whatever the effect, it is unlikely to be large. A randomised controlled trial of the effects of digoxin on survival, despite its superior ability to control for other factors, would need to be extremely large to detect an effect that is not shown by these data.

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Rapid plasma digoxin assay in outpatients—a useful routine technique?

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SUMMARY In 25 outpatients taking digoxin for chronic atrial fibrillation (established for at least six months) a prospective study identified only one case in which rapid availability of the results of a plasma digoxin assay altered the dose which had already been selected on the basis of simple clinical assessment. No patient received more than 375 µg digoxin per day and none showed clinical evidence of toxicity even though seven had renal impairment. Six other patients had poorly controlled ventricular rates requiring larger doses of digoxin, but even in these patients the dose could be selected on clinical grounds alone. Despite the availability of a very rapid fluorescence polarisation immunoassay for digoxin, simple but careful clinical monitoring is an adequate basis for the selection of a suitable dose in most patients taking digoxin for atrial fibrillation.

Radioimmunoassay of plasma digoxin provides clinically valuable information, although the correlation between digoxin concentration and clinical state is imperfect, particularly at each end of the suggested therapeutic range.¹ The 3 to 4 hour assay time means that further clinic visits or advice by letter or telephone are required by outpatients.

Fluorescence polarisation immunoassay of plasma digoxin concentration takes about 20 minutes² so that clinicians can review treatment at a single clinic visit. The value of rapid outpatient assays of anti-convulsant drugs has been established,³ but in other circumstances the availability of a rapid assay may lead to its overuse.⁴ We have assessed the clinical usefulness of a rapid plasma digoxin assay for patients attending a district general hospital cardiological clinic.

Patients and methods

We studied 25 euthyroid outpatients aged 50 to 86 years with chronic rheumatic or ischaemic heart disease complicated by atrial fibrillation. The presence of the arrhythmia was confirmed by an electrocardiogram on the study day. In every patient the serum albumin concentration was normal. All

patients had taken the same dose of digoxin at night for at least four weeks and had taken a prestudy dose around midnight. A blood sample was taken at 9 am the following morning at the clinic.

We used a brief standard questionnaire to assess dose adequacy as low, high, or optimum. An optimum response was defined as an absence of palpitation or symptoms of toxicity¹ with a resting ventricular rate of 60 to 100 beats per minute. If a dose was thought to be inadequate a proposed increase was recorded. One hour later this clinical assessment was reviewed in the light of plasma potassium and creatinine concentrations, and again when the plasma digoxin concentration was known, to see whether the proposed digoxin dose should be changed. When a dose was increased the procedure was repeated after four weeks.

The Abbott TDX fluorescence polarisation immunoassay method was used to measure plasma digoxin. The therapeutic range eight to 10 hours postdose is 1.2 to 2.4 nmol/l with this assay.

Results

Thirty two measurements of plasma digoxin were obtained in 25 patients (see Table). All the patients were normokalaemic, though 20 were taking diuretics. Seven had renal impairment (creatinine 120–200 µmol/l) but their digoxin doses varied

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Accepted for publication 4 June 1985.

Table Relation between plasma digoxin concentration and heart rate

Case No	Previous heart rate over 120 beats per min	Initial assessment		Increased dose	
		Heart rate	Digoxin (nmol/l)	Heart rate	Digoxin (nmol/l)
1	Yes	124	0.38	84	0.95
2	Yes	122	0.35	92	1.30
3	Yes	120	1.42	70	2.64*
4	Yes	118	0.75	96	1.45
5	Yes	112	0.60	90	0.99
6	—	108	0.52	78	0.72
7	—	98	1.25	—	—
8	—	92	0.35	80	0.95
9	—	90	0.62	—	—
10	—	88	0.64	—	—
11	Yes	86	0.82	—	—
12	Yes	78	1.40	—	—
13	Yes	78	1.15	—	—
14	Yes	70	1.30	—	—
15	—	70	0.74	—	—
16	—	65	1.25	—	—
17	Yes	62	2.82*	—	—
18	—	60	1.42	—	—
Creatinine above 120 $\mu\text{mol/l}$					
19	Yes	98	1.36	—	—
20	Yes	88	2.40	—	—
21	Yes	84	1.10	—	—
22	—	82	1.20	—	—
23	Yes	78	2.52*	—	—
24	—	68	1.46	—	—
25	Yes	62	1.82	—	—

* Concentrations above therapeutic range.

across the whole range seen in the study (62.5 μg on alternate days to 375 μg daily) and none showed signs of digoxin toxicity. Knowledge of plasma creatinine and potassium concentrations did not indicate that the proposed maintenance dose should be altered.

All patients in whom heart rate was thought to be less than optimally controlled (cases 1–6) were given an increased digoxin dose and the subsequent response was adequate. In no case did knowledge of the digoxin concentration lead to a change in the proposed management, even in case 3, in whom the initial concentration was in the therapeutic range.

In one of the 19 optimally controlled patients (case 8) the finding of a digoxin concentration of 0.32 nmol/l did alter management since despite a resting heart rate of 92/min on 125 μg daily the patient complained of mild palpitation; this was abolished when a daily dose of 250 μg was given and plasma digoxin was 0.95 nmol/l.

Cases 3, 17, and 23 had concentrations just above the therapeutic range but all were well and remained so for at least another four weeks.

Discussion

Two centuries after Withering's report on digitalis⁵ our small study further emphasises the importance of clinical observation in the use of digoxin. In only one patient in 25 (and one measurement in 32) did the knowledge of a plasma digoxin concentration

influence management. Thus, in contrast to the situation with anticonvulsants, which have a similarly narrow therapeutic ratio and fickle reputation, we cannot advocate widespread adoption of a same visit outpatient service for routine digoxin assay for patients with atrial fibrillation attending follow up clinics such as ours.

Retrospective studies have suggested that while clinical judgement should remain the cornerstone of therapy with digoxin, knowledge of plasma concentrations may assist when toxicity is suspected, when atrial fibrillation is refractory to a reasonable dose of digoxin, and when renal function is impaired.⁶ In our study only five concentrations exceeded 1.5 nmol/l, so it is not surprising that plasma digoxin concentration was not a useful indicator of toxicity. Initially we were surprised to find that no patient showed clinical evidence of toxicity; in the early 1970s we would have expected to find that about 25% of patients had evidence of digoxin toxicity.¹⁶ A cautious dose selection policy was shown in the current study—42 of 68 similar patients described in 1970 were taking more than 375 μg a day, the maximum dose used in our study.⁶

Although we might have expected to find a knowledge of digoxin concentrations useful in six patients who were "under-digitalised" at follow up, their management based on clinical information was satisfactory. Furthermore, four of seven patients with optimal heart rates but digoxin concentrations below

1 nmol/l had demonstrated benefit from digoxin. Cases 5, 6, and 8 had needed an increased dose of digoxin during the study and case 11 had a documented fast ventricular response rate before digoxin was started. Modest doses of digoxin may result in very low plasma digoxin concentrations but some patients will still respond adequately.

In view of our policy of cautious dose selection, it is not surprising to find that in our seven patients with moderate renal impairment no benefit was derived from a knowledge of plasma digoxin concentration despite the risk of toxicity.

We do not of course deny the potential value of the rapid assay in apparently refractory atrial fibrillation or in patients with evidence of toxicity or where there is the suspicion of poor compliance.

Our conclusion depends in part upon the current dose selection policy which is more conservative than that used 15 years ago; our data imply that this policy is reasonable provided physicians continue to apply their clinical senses with the diligence shown by Withering two centuries ago.⁵

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Withering bicentennial celebrations



The chairman and speakers at the William Withering commemoration meeting, organised jointly by the Association of Physicians and British Cardiac Society, held on 18 April 1985.

From left to right: CT DOLLERY, SV PERRY, SIR RAYMOND HOFFENBERG, PRCP, D G GIBSON, W LITTLER, SIR MELVILLE ARNOTT, D NOBLE, D M KRIKLER, A GUZ, F L MEIJLER, M F OLIVER, H B BURCHELL, and T W SMITH.

British celebrations

On 18 April 1985 the Association of Physicians of Great Britain and Ireland and the British Cardiac Society held a joint meeting in Birmingham to commemorate the two hundredth anniversary of the publication of William Withering's *An Account of the Foxglove*. The chairman of the meeting was Sir Raymond Hoffenberg, PRCP, William Withering Professor of Medicine at the University of Birmingham. The sessional chairmen were Michael Oliver, Sir Melville Arnott, and Howard Burchell, and Sir Raymond, who presided over the final scientific session, the William Withering Lecture of the Royal College of Physicians, given by Colin Dollery (p 234). Speakers in the scientific sessions were Thomas Smith, Denis Noble, Victor Perry, Dennis Krikler, William Littler, Frits Meijler, Abe Guz, and Derek Gibson; last minute indisposition

prevented the participation of Charles Fisch. Abstracts of the papers appeared in the *British Heart Journal* 1985; 53: 686-7 but do not include the contributions of Littler, Meijler, Guz, and Gibson which were part of a debate under the chairmanship of Burchell. After the scientific proceedings, participants gathered at Edgbaston Parish Church, in whose yard Withering is buried, for an address by George Whitfield (p 253) and an orchestral recital. This was followed by a reception at Edgbaston Hall, Withering's old home, in whose grounds the foxglove still grows.

American celebrations

At its scientific sessions at Anaheim, the American College of Cardiology held a half-day meeting on 12 March 1985 to commemorate the publication of *An*

Account of the Foxglove, with Charles Fisch as chairman and Dennis Krikler as co-chairman. Eugene Braunwald delivered the American College's William Withering Lecture entitled "Effects of cardiac glycosides on the contractility of the normal and failing heart". The papers presented at this meeting,

together with other invited contributions, have been published as a supplement to the May 1985 issue of the *Journal of the American College of Cardiology* with Dr Fisch as guest editor. The flyleaf of the supplement is adorned by a colour photograph of *Digitalis lanata* by Frits Meijler.

Bicentenary of *An Account of the Foxglove* *Historical address given at Edgbaston Parish Church, Birmingham**

A G W WHITFIELD

From the University of Birmingham, Birmingham

In a period of less than 30 years' practice William Withering achieved a reputation unsurpassed by any physician before or since. The very large gathering at his funeral in this church on 10 October 1799 and the mural tablet leave no doubt as to the high opinion in which he was held during his lifetime. A verse at his death may well have been thought euphemistic and sentimental:

"Deep in the earth, the debt of nature paid
The mortal part of Withering is laid
And though he seems to share the common lot
Of those who perish and are soon forgot,
His fame will never die! Each future age
Instructed by the labours of his page
Shall hail his honoured name with grateful praise
And bards his skill record in tuneful lays
Of wealth or power short is the transient state
Whilst science soars above the reach of fate!"

How prescient this unknown poet was, for here today, 200 years after the publication of *An Account of the Foxglove*, members of the Association of Physicians of Great Britain and Ireland and the British Cardiac Society together with leaders in cardiology from abroad have spent five hours hotly debating the use of digitalis and a longer period honouring Birmingham's greatest physician and its patron saint of medicine.

Each new drug goes through three major phases. In the first it is the cure for everything and it is criminal not to prescribe it; in the second it is so dangerous that it should be used only by experts, which of course excludes everyone but the speaker; in the third its sphere of usefulness becomes more clearly defined and control of dosage and other factors help to minimise unwanted effects. Today has shown that digitalis, despite its double century, has not yet reached the haven of phase three.

It is said that the major requirements for success in life are high intelligence, great energy, and an ability to establish and maintain harmonious

relationships with everyone around. Withering's intellectual excellence and capacity for work are beyond question; in fact it is difficult to know how a man suffering from progressive phthisis could cope with such a huge practice and so many other scientific interests including botany, chemistry, and mineralogy. What he lacked was the knack of getting on with all comers. In fact he needed no lessons from Whistler in "the gentle art of making enemies." But despite this he prospered; his scientific and professional contribution was immense and his difficulty in personal relationships may in part have been due to his physical illness.

He was the only son of wealthy parents, Edmund Withering the Wellington apothecary and his wife Sarah, who was the daughter of George Hector, the Lichfield general practitioner, and the sister of Brooke Hector, the Lichfield physician, and Edmund Hector, the noted Birmingham surgeon. William Withering had two sisters. The elder, Mary, is thought to have been mentally subnormal and died early; the younger, Sarah, never married. It can be seen therefore how William became spoilt and developed personal qualities of the type we are now accustomed to see on the centre court at Wimbledon.

When Withering left Stafford Mr John Eld, who was largely responsible for getting the infirmary built, and Mr Hughes the secretary could not have been kinder but Withering did his best to pick a quarrel with them. He undertook to travel weekly from Birmingham to the infirmary until his successor was appointed, but the General Board arranged for his colleague at Stafford, Dr Campbell, to assume responsibility. After a petulant letter from Withering the Board let him have his way.

Erasmus Darwin, of Lichfield, as well as being a most able and successful physician, was a very knowledgeable botanist and had an eight acre botanic garden at Abnalls. He had great influence and this secured for Withering the vacancy left in Birmingham by Dr Small's death. He was a kind,

*Given on 18 April 1985 as part of the William Withering commemoration meeting.

benevolent, and generous man and was anxious to help Withering in any way possible, and when Withering was completing his book on British botany Darwin suggested that a short title such as "The Scientific Herbal", "Linnaean Herbal", or "English Botany" would help it to sell. Withering took offence at this suggestion and entitled it *The Botanical Arrangement of all the Vegetables naturally growing in Great Britain. With descriptions of the genera and species according to the system of Linnaeus with an easy introduction to the study of Botany*, an appellation by no means short! It was a poor effort being little more than a translation from Carl Linnaeus's *Genera plantarum* of the species found in Great Britain. The second edition in 1787–92 was a great improvement thanks to the generous help of Dr Jonathan Stokes, but Withering quarrelled with him and they both called in solicitors to act for them.

The rift between Withering and Darwin gradually became deeper and for this they were both to blame. Withering continued to nurse an imaginary grudge and Darwin began to retaliate. His brilliant medical student son Charles died at the age of 19 in Edinburgh from septicaemia due to a dissecting room wound and Darwin published his prize essay and medical dissertation together with a biographical memoir and an account of five patients treated with digitalis. The description of the five patients was almost certainly not written by Charles but was added by Erasmus. It was the first published description of the therapeutic use of digitalis and it infuriated Withering who was preparing *An Account of the Foxglove* and regarded it as his discovery. In addition, early in 1785 Darwin gave a paper entitled "An Account of the Successful Use of Foxglove in some Dropsies, and the Pulmonary Consumption" and it was later published in *Medical Transactions*. Another publication in 1785 from the Lichfield Botanic Society comprised an English version of Linnaeus's *Systema vegetabilium*. It was dedicated to Sir Joseph Banks, the President of the Royal Society, and favourably reviewed in the *Monthly Review*. This provoked cries of protest from Withering to the Editor, Dr Ralph Griffiths, for Withering knew that the Lichfield Society consisted only of Darwin and two others, Sir Brooke Boothby and Mr William Jackson.

The quarrel reached its height in 1788 when Mr Cartwright, a Wellington apothecary, called in both Robert Darwin, Erasmus's physician son from Shrewsbury, and Withering to see the same patient. They did not meet but there was increasingly discourteous correspondence and criticism one of each other. Mrs Frances Houlston, the patient, was a successful purveyor of religious tracts and she had some febrile abdominal illness which Withering diagnosed

as hepatitis. Despite being fought over by two Fellows of the Royal Society and a third in the background striving to manipulate the scene, the patient recovered and lived another 40 years. Perhaps the devil does look after his own.

Though Erasmus Darwin's conduct was by no means always correct he would have understood what Bertrand Russell meant when he said "I can't think why he dislikes me. I never did him any kindness."

Withering was fortunate in that he never had any financial worries. His parents were wealthy and he did not marry until a little over two years before he came to Birmingham and from the moment of his arrival his professional income was enormous. His first child, a daughter Helena, died when she was a little over a year old, though from what is not known. His second daughter, Charlotte, married Beriah Botfield when she was 28 and had but one child. His only son William took a degree at Edinburgh but confined his activities to publishing his father's memoir and republishing his books. The son lived at the Larches in Sparkbrook until 1820 when he moved to Wick House, Brislington, near Bristol dying there (not from overwork) in 1832 aged 56. His widow Lydia (née Rickards) continued to live there until 1867, when she died from senile dementia aged 82. There were no grandchildren and the name of Withering disappeared.

When Withering first came to Birmingham in 1775 he lodged with Mr Wheeley, a coachbuilder, at Number 10 The Square and had his consulting rooms at 9 Temple Row. Later he bought Number 15 The Square and also on part of a nearby plot of land which he purchased he built the Stone House in Corbett's Alley. In 1786 he took a 14 year lease of Edgbaston Hall and Park from Sir Henry Gough, living there until six days before his death when he moved to the Larches in Sparkbrook, which he had bought earlier that year from Mr W M Humphreys then of Cheltenham. None of these houses could be described as humble cottages.

In 1791 Edgbaston Hall was in grave danger of being sacked and burned by the rioting mobs. Many of its most valuable contents were moved into this church or elsewhere for safety and the assailants were bribed and plied with drink so that they became incapable of further action. Eventually the army arrived from Nottingham and quelled the riots but not before extensive damage had been done to houses in and around the city, but Edgbaston Hall itself escaped. Edgbaston Hall has stood on its present site since the Norman Conquest. It was destroyed during the Civil War but was rebuilt in 1717, the building being altered and modernised in 1852 by Sir Charles Barry. The reception after this service will be held

there and you will see that though it is now a golf clubhouse it is still quite an impressive building.

Withering's tuberculosis had been present for at least 23 years when he died: he suffered considerable fever, pleurisy, cough, and sputum, particularly during the winter, and in his later years he was much disabled by dyspnoea. He spent the winters of 1792-3 and 1793-4 in Portugal in the vain hope of climatic benefit, and when he returned to Edgbaston Hall in 1794, with Matthew Boulton's help, he contrived a form of air conditioning which kept the indoor temperature at about 65°F. In the winter he rarely went out and these measures undoubtedly prolonged his life. It is sad to think that among his many patients there must have been some who contracted tuberculosis from him but the infective nature of the disease, though suspected, was unproven until long after Withering's death.

The famous portrait of William Withering by Carl Frederik von Breda was painted in 1792 when von Breda was in England as court painter. The original is in the National Gallery at Stockholm but an excellent engraving from it was produced by W Bond and appeared as a frontispiece in *Miscellaneous Tracts* and Ridley made another for Thornton's collection. Many present here tonight will have seen the copy of the original painting in the Dean's room at our medical school. It was presented by K D Wilkinson with a hanging brass plaque describing the donor as "Professor of Pharmacology and Therapeutics in the University of Birmingham 1929-47 at a salary of £25 per annum." When A P Thomson became Dean,

Wilkinson had died and the plaque so wounded AP's warm heart that he had it replaced by one which omits all financial details.

What of Withering as a man? He was certainly highly intelligent and an obsessional worker. He had a breadth of scientific interest remarkable in a physician with such a huge practice, and for a man so preoccupied with seeing patients he was a good husband and father even though he did not teach his son to work. Why he wanted such a large practice is uncertain. His motives may have been entirely altruistic, but perhaps despite his comfortable financial circumstances he may have been imbued with a desire for greater wealth. He was certainly a difficult colleague, prickly and quarrelsome, and if he knew any amusing stories he kept them to himself.

The two great eighteenth century midlanders, Withering, who worshipped in this church, and Samuel Johnson, who was a diligent attender at St Mary's, Lichfield, and St Clement Danes in the Strand, were men of strong religious conviction. One cannot, however, imagine Withering capable of uttering the famous "scruples" prayer which typifies Johnson's humility and endeared him to so many:

"Enable me to break the chain of my sins, to overcome vain scruples and to use such diligence in lawful employment as may enable me to support myself and do good to others. O Lord forgive all the time lost in idleness; pardon the sins which I have committed, and grant that I may redeem the time misspent and be reconciled to thee by true repentance that I may live and die in peace."

Withering and the foxglove: the making of a myth

DENNIS M KRIKLER

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The bicentennial celebrations are prompted not by Withering's original observation of the clinical value of digitalis in 1775 but rather by the publication of his detailed report 10 years later. This book is the source of the information on how he came to learn of digitalis.¹ As indicated elsewhere,² the circumstances of his encounter with digitalis could not be more clearly set out, and alternative explanations seem redundant. Peck and Wilkinson³ surmised that Withering's interest in digitalis arose after he had moved from Stafford to Birmingham, during the period when he returned to Stafford each week to keep an eye on patients until his successor arrived. They speculated that he had encountered a patient with dropsy, and that on a subsequent journey he inquired after her and discovered that she had done remarkably well on secret herbs. There is however no prior reference to justify this statement, which can be looked upon as a harmless speculation. Roddis⁴ had earlier recounted the story in exactly the terms used by Withering, but several years before this an alternative explanation had been created. The origin of this vivid account has been difficult to track down, and the story entered medical awareness as the introductory note by Willius and Keys to their extract⁵ from Withering's book *An Account of the Foxglove*.¹

Where did Willius and Keys derive their information? They clearly state that the picture that they published was an imaginative rendering, as indeed it must have been, for it is said to depict Withering at the time of his "discovery" of digitalis (Figure), but in 1775 he was 34 years old, and in sound health; his chronic lung disease only became apparent 8 or 9 years later. Willius and Keys attributed the picture to Parke, Davis and Company, but the original painting is no longer in their collection, nor could it be found in the Detroit Historical Museum or in the Burton Collection at the Detroit Public Library (J A Callahan, N Hensel, and H B Burchell, personal communication). Direct enquiries to Parke-Davis, now a division of the Warner-Lambert Company, did not at first yield the answer, but one of their senior staff soon chanced

upon a stack of 250 pictures of advertisements used by them between the late 1920s and the 1940s, only 100 feet from his office (J A Controulis, personal communication). The picture shown in the Figure is the 23rd in the series and was painted by Will Meade Prince in 1928 or 1929; while many in the set carry his signature in the lower right hand corner, this had been removed from the present picture as well as some others to provide what was considered to be an "appropriate fit for the advertising copy".

The enthusiastic text that accompanied the picture is of almost as much interest as the creation of the scene. Perhaps Will Meade Prince felt entitled to make Withering look older because he was under the impression that his scientific discovery was made in 1785, but even then he would have been only 44. He is said to be handing over "golden sovereigns for the secret of the wayside flower" to Old Mother Hutton, a "Shropshire herb-woman" who had guarded her secret jealously. Correctly, they mentioned the fact that digitalis had previously proved helpful when given to the Dean of Brazen Nose College, Oxford, for his dropsy. Though Withering himself mentions 20 or more herbs, the advertisement refers to 12. Though Withering, an expert botanist, had indicated that by glancing at the prescription he could see that the foxglove must have contained the only possible active substance,¹ the advertisement more dramatically claimed that "after long and patient trial he found 11 of them medicinally worthless. But from the twelfth, the purple foxglove, he obtained a powerful new drug . . . digitalis."

Thus the name Old Mother Hutton, the creation of a copywriter, has crept in and become linked with the discovery of the medicinal properties of digitalis, and an interesting anecdote turns out to be an embellishment rather than an improvement on the story as given by Withering.¹

A relevant sidelight: soon after Parke, Davis & Company ran their series of historical advertisements, one of the original members of their present parent organisation, William R Warner & Company, adorned their physicians' diary with historical footnotes that provided many with their first exposure to famous names and events in medicine and surgery.

Requests for reprints to Dr Dennis Krikler, Cardiovascular Division, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London W12 0HS.



Figure Depiction by Will Meade Prince of William Withering exchanging golden sovereigns for the "secret recipe" held by "Old Mother Hutton" (published with acknowledgement to Parke-Davis, Morris Plains, New Jersey).

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Plants and cardiac glycosides

A HOLLMAN

From the Cardiac Department, University College Hospital, London

It is often asked why plants contain such remarkable compounds, sometimes beyond the practical reach of the synthetic chemist. What use are these compounds to the plant itself? Defence against predators is one answer although it has to be said that many of today's predators did not exist when the flowering plants, the angiosperms, evolved 80-100 million years ago. It has been shown for example that the methylxanthines in tea and coffee have static and cidal activity against insect pests.¹

Glycosides are usually compounds of plant origin. They are made up of one or more sugars combined with an alcohol, a phenol, or a complex molecule such as a steroid nucleus. The non-sugar moiety or aglycone is also called a genin. Because they do not contain nitrogen it is wrong to call them alkaloids. In addition to the cardiac glycosides with their cyclopentanoperhydrophenanthrene nucleus in the genin moiety there are other glycosidal plant substances such as the anthraquinone derivatives senna, rhubarb, aloe, and cascara; saponins; cyanogenetic glycosides such as amygdalin from bitter almond; terpene and sterol glycosides; glycosidal dyes and pigments; and finally gums and tannins. The venom glands of the skin of the toad (*Bufo*) contain digitalis like compounds and this animal gives its name to that group of the glycosides which have a steroid skeleton of 24 carbon atoms (C₂₄), the bufadienolides. A few plant glycosides also belong to this group, notably those from squill, but all others have a C₂₃ skeleton and belong to the cardenolides group.

The genus *Digitalis* is named after the shape of the flowers (*digitus*, a finger). Although ingenious alternatives have been proposed to explain the common name, foxglove, there is no doubt that this title does mean the glove of a fox. The genus comprises biennial or perennial herbs, or rarely small shrubs, with leaves which are simple, arranged alternately, and sometimes with the lowest leaves forming a rosette. They are natives of Europe, North Africa, and West Asia but not of China. The formerly named

D chinensis has been reclassified as *Adenosma grandiflorum*. The showy flowers are purple, yellowish brown, or white, carried in terminal racemes. The calyx has five equal lobes and there are four stamens. Other characteristics are variable and on the basis of these differences the genus is divided into twelve species and seven subspecies. The full taxonomy² of *Digitalis* is as follows: class, Angiospermae; subclass, Dicotyledon; superorder, Asterales; order, Scrophulariales; family, Scrophulariaceae; subfamily, Rhinanthoideae; tribe, Digitalideae; genus, *Digitalis*. *D purpurea* is the only species native to Britain. It is also found in Western Europe and is a complex polytypic species with at least three subspecies. The flowers are purple, pale pink, or white and being usually calcifuge it is rare in calcareous districts such as Cambridgeshire and the Jura. The species *D lanata* which comes from Hungary, Romania, and the Balkan peninsula has white or yellowish white flowers with brown or violet veins and was introduced to Britain in 1789. This species is named after its characteristically downy flowers. Other species³ include *D obscura*, *D thapsis*, *D dubia*, and *D parviflora* from Spain; *D viridiflora* and *D laevigata* from the Balkan peninsula; *D lutea*, *D grandiflora*, and *D ferruginea* from western, eastern, and southern Europe respectively; *D leucophaea* from northern Greece; *D orientalis* from the Levant; *D sibirica* from Siberia.

The native glycoside is susceptible to hydrolysis by enzymes during the extraction process. The acetyl group and glucose are split off, but fortunately the partly hydrolysed glycosides such as digoxin and digitoxin are as biologically active as the parent compound. Were this not so the action of digitalis might never have been established since the native compounds were first isolated by A Stoll as late as 1935. The native compounds in *D lanata* are lanatosides A, B, and C which yield digitoxin, gitoxin, and digoxin (Table 1). *D purpurea* has purpurea glycosides A and B but no glycoside corresponding to lanatoside C. Digitoxin comes from *D ferruginea*, *D grandiflora*, *D lanata*, *D lutea*, and four varieties of *D purpurea*. Digoxin comes from *D grandiflora*, *D lanata*, and *D orientalis*.

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It was the poisonous nature of other plants which contain cardiac glycosides which first drew attention to them not the typical chemical structure of the glycosides that they contain. In 1898 Lauder Brunton wrote, "various drugs stimulate the vagus roots in the medulla oblongata or the terminal endings of the heart itself ... many of the arrow poisons and ordeal poisons act on the heart in this way, among them are strophanthus, erythrophloeum, tanghinia, manganja, carraval, vao, oleander, squill, hellebore ...".⁴ Many plants contain cardiac glycosides and some species contain up to six. One glycoside may be present in several species; strophanthidin for example is found in 10 genera from 7 families.

There are 36 cardiac genins of plant origin and they are divided into six groups according to their accompanying sugars. There is no obvious pattern for the occurrence of glycosides in different plants.

They occur both in monocotyledons (for example Liliaceae) and in dicotyledons, and their geographical distribution is irregular, as is the distribution of other important plant medicines. For example, podophyllotoxin from which the anticancer drug etoposide is derived is found in two *Podophyllum* species, one from the Himalayas and the other from North America. Because the taxonomy of plants according to their chemical composition is not fully developed, the list of the families and their genera which contain cardiac glycosides given in Table 2 is based on the Linnaean classification.⁵

A few glycosides and plants may be picked out for special mention. Ouabain, which is ineffective when given by mouth, comes from the wood of *Aconanthera schimperi*, the Ouabaio tree, and also from the seeds of *Strophanthus gratus*. It is more familiar to pharmacologists than to clinicians, as is strophanthin K a glycoside mixture from *Strophanthus*



Digitalis purpurea (L) (Source: Curtis W. *Flora Londinensis*, Vol 1. London, 1777.)



Digitalis lanata (Ehr) (Source: Lindley J. *Digitalium monographia*. London, 1821.)

Table 1 Botanical sources and major chemical components of cardiac glycosides of clinical importance

Plant source	Precursor glycoside	Split off by enzymatic and mild alkaline hydrolysis*	Glycoside	Split off by acid hydrolysis*	Aglycone or genin
<i>Digitalis</i>					
<i>D. purpurea</i> (leaf)	Purpurea-glycoside A (deacetyldigilanid A)	Glucose	Digitoxin	Digitoxose (3)	Digitoxigenin
	Purpurea-glycoside B (deacetyldigilanid B)	Glucose	Gitoxin	Digitoxose (3)	Gitoxigenin
	—	—	Gitalin	Digitoxose (2)	Gitaligenin (gitoxigenin hydrate)
<i>D. lanata</i> (leaf)	Lanatoside A (digilanid A)	Glucose + acetic acid	Digitoxin	Digitoxose (3)	Digitoxigenin
	Lanatoside B (digilanid B)	Glucose + acetic acid	Gitoxin	Digitoxose (3)	Gitoxigenin
	Lanatoside C (digilanid C; cedilanid)	Glucose + acetic acid	Digoxin	Digitoxose (3)	Digoxigenin
	—	—	—	—	—
<i>Strophanthus</i>					
<i>S. kombé</i> (seed)	K-strophanthoside	Glucose	K-strophanthin-β (strophanthin)	Glucose + cymarose	Strophanthidin
	K-strophanthoside	Glucose (2)	Cymarol	Cymarose	Strophanthidin
	K-strophanthin-β	Glucose	Cymarol	Cymarose	Strophanthidin
<i>S. gratus</i> (seed)	—	—	Ouabain (G-strophanthin)	Rhamnose	Ouabagenin (G-strophanthidin)
	—	—	—	—	—
<i>Scilla (squill)</i>					
<i>Urginea maritima</i> or <i>indica</i> (bulb)	Scillaren A	Glucose	Proscillaridin A	Rhamnose	Scillaridin A

* One mole of sugar or acetic acid is split off, unless the number of moles is otherwise indicated in parentheses.

(From *The Pharmacological Basis of Therapeutics*. Goodman LS, Gilman A. 5th ed. Macmillan, New York, 1975. Reproduced by permission of the authors and publisher.)

Table 2 Families and genera containing cardiac glycosides

APOCYNACEAE	LILIACEAE
<i>Acokanthera</i>	<i>Bowiea</i>
<i>Adenium</i>	<i>Convallaria</i>
<i>Apocyanum</i>	<i>Ornithogalum</i>
<i>Carissa</i>	<i>Rohdea</i>
<i>Cerbera</i>	<i>Urginea</i>
<i>Nerium</i>	
<i>Strophanthus</i>	
<i>Tanghinia</i>	MORACEAE
<i>Thevetia</i>	<i>Antiaris</i>
	<i>Antiaropsis</i>
	<i>Castilla</i>
	<i>Ogcodeia</i>
ASCLEPIADACEAE	
<i>Asclepias</i>	LEGUMINOSAE
<i>Calotropis</i>	<i>Coronilla</i>
<i>Cryptostegia</i>	
<i>Gomphocarpus</i>	
<i>Menabea</i>	RANUNCULACEAE
<i>Pachycarpus</i>	<i>Adonis</i>
<i>Periploca</i>	<i>Helleborus</i>
<i>Xysmalobium</i>	
	SCROPHULARIACEAE
	<i>Digitalis</i>
	<i>Isoplexis</i>
CELASTRACEAE	
<i>Euonymus</i>	STERCULIACEAE
	<i>Mansonia</i>
CRUCIFERAE	
<i>Cheiranthus</i>	TILIACEAE
<i>Erysimum</i>	<i>Corchorus</i>

kombé seeds. Since the times of the ancient Egyptians and Romans, squill from the bulb of the white or mediterranean squill, *Urginea maritima*, has been used as a diuretic and expectorant (and in large doses as an emetic and purgative). It had fame as a constituent of Guy's pill, in which it was combined with one grain each of prepared digitalis and mercury blue pill. Its active principles are scillarin A and B. Oleander is the glycoside in the mediterranean oleander or rose bay, *Nerium oleander*. This plant has caused accidental poisoning with heart block in Australian children (J B Hickie, personal communication), and people have died after eating food cooked on oleander wood fires. Several glycosides come from the lily of the valley, *Convallaria majalis*.

Gardeners will have already recognised the generic names of the star of Bethlehem, wallflower, and Christmas rose, while gourmets will be relieved to learn that although the family Moraceae is included, the mulberry, *Morus nigra*, does not contain cardiac glycosides. Many large plant families do not have any members containing cardiac glycosides. One example is the family Rosaceae to which the hawthorn, *Crataegus monogyna*, belongs. This plant, however, contains a flavinoid glycoside which has a weak digitalis like action.



Urginea maritima (Baker) (Source: Redouté P J. *Les Liliacées*, Vol 2. Paris, 1805.)

Anticipating by 100 years Pasteur's dictum, "dans les champs de l'observation, le hasard ne favorise que les esprits préparés . . .", it was certainly chance acting on Withering's prepared mind that gave *Digitalis purpurea* its scientific start in therapeutics, but many other species contain cardioactive principles and it is to be hoped that more will be discovered among the world's 250 000 species, unless the accelerating pace of tropical deforestation eliminates a species before we have studied it.

I thank Mrs Gina Douglas, Librarian to the Linnean Society of London, for her help.



Nerium oleander (L.) (Source: Sibthorp J. *Flora Graeca*, Vol 3. London, 1819.)

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Cultivation and breeding of *Digitalis lanata* in the Netherlands

C MASTENBROEK

From the Stichting "Kruidentuin te Doornspijk", Elburg, The Netherlands

SUMMARY After the second world war Marshall Aid funds were used to establish a cooperative organisation for growing, drying, and selling *Digitalis lanata* (and other medicinal, aromatic, and culinary herbs) in the Netherlands. The crop is sown in mid April and the fully mechanised harvest of the leaves takes place from September to late November. The leaves are dried for 10-12 hours at 50°C maximum. The aim of breeding trials is to improve leaf production, erect leaf attitude, resistance to *Septoria* leaf spot and to bolting, and a higher dry matter and digoxin content.

Cultivation

It is cheaper for the pharmaceutical industry to extract digoxin from the dried leaves of *Digitalis lanata* than to synthesise the drug chemically. *D lanata* (Fig. 1a) is called the woolly foxglove because the calyx of the flower is thickly covered with white glistening slightly sticky hairs (Fig. 1b). *Digitalis purpurea*, which is native to north west Europe, was grown for the extraction of digitoxin until the medical superiority of digoxin was demonstrated. Digoxin only occurs in *D lanata*, which is not native to north west Europe; its natural habitat is south east Europe.

After the second world war the Dutch government used some Marshall Aid funds to promote the cultivation of *D lanata* (and other medicinal plants and aromatic and culinary herbs). Several cooperative drying plants were established; three of these are still active. They are situated in the north east, centre, and south east of the Netherlands. In 1984 230 hectares of *D lanata* were harvested and dried. Contracts with growers are arranged by the three regional drying factories and a central cooperative VNK (Verenigde Nederlandse Kruidencoöperatie, United Dutch Herb Cooperative) organises contracts with and delivery to the pharmaceutical industry.

D lanata is cultivated on peaty, sandy, and clay soils. The seeds are drilled in mid-April with machines adapted to sow very small quantities (2 kg per hectare) of tiny seeds. Germination is very slow, and it takes about two months before the seedlings

develop sizeable leaves. The leaves (Fig. 2) are harvested from the end of September till the middle of November or even later, depending on weather conditions. Harvesting is completely mechanised. The mean yield of fresh leaves is about 30 tonnes per hectare. The freshly cut leaves are immediately transported to the drying factories. After weighing they are coarsely cut, washed to remove soil particles, and dried for 10-12 hours at 50°C until their moisture content is 8-10%. The dried product, around 5 tonnes per hectare, is pressed into polyethylene bags (35 kg per bag) and exported mainly to the United Kingdom, the United States of America, Germany, and France.

Breeding

The growers, drying plants, and pharmaceutical industry all have an interest in the improvement of the inherited properties of the species. Their various priorities are set out below.

THE GROWERS

The yield of fresh leaves is the basis for payment. The farmer wants to grow a variety that produces a heavy leaf canopy. The first step in breeding, therefore, is selection of individual plants with many broad and long leaves. Until about 10 years ago the material cultivated had been obtained through natural accession from a botanical garden and did not have outstandingly large leaves (Fig. 3a). Individual plants with larger than average leaves were selected and grown for their seed. In the next generation the plant type appeared to have been somewhat improved. Variation was still apparent and this was

Requests for reprints to Dr C Mastenbroek, De Terminator 8, 8251 AD Dronten, The Netherlands.

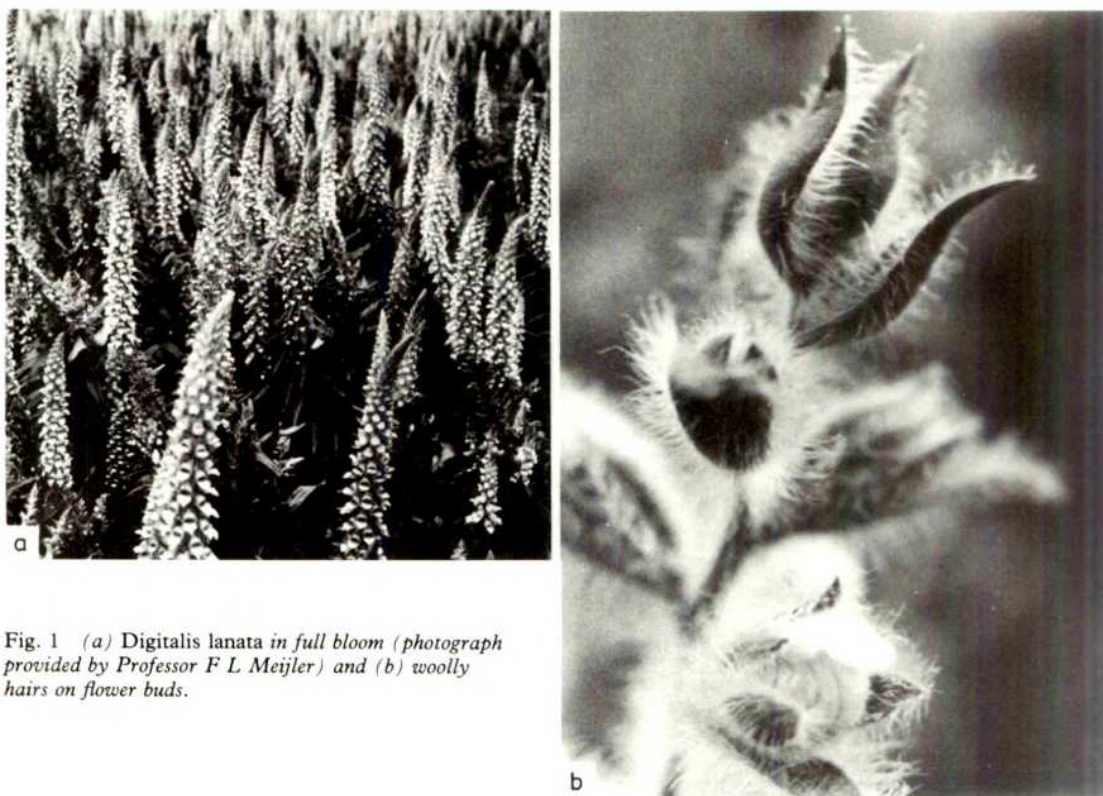


Fig. 1 (a) *Digitalis lanata* in full bloom (photograph provided by Professor F L Meijler) and (b) woolly hairs on flower buds.

again exploited for the selection of better plants. Selection over three consecutive generations has considerably improved the plant type (Figs. 3b and c). It should be borne in mind, however, that in a well established production field more than 1 000 000 plants are competing for room, light, and nourishment, and this competition means that plants of the same genetic constitution will have a different appearance when they are grown in closed stands and as spaced plants in nurseries. The yields of individual plants will also differ considerably according to their growing conditions; nevertheless there is evidence that selection has improved leaf yield by about 15%.

The leaf attitude of the original accession tended to be prostrate, and some of the lower leaves remained attached to the plant after harvesting (Fig. 4). The leaves left behind can only be used as green manure and represent a loss in income to the grower. An upright leaf attitude is therefore an advantage. Selection has produced a plant type with a strikingly erect leaf habit. This improvement is more apparent when *D. lanata* is grown in nurseries of spaced plants rather than in close stands in production fields. Plants with erect leaves will tend to produce a cleaner harvested

product since the more upright the leaves are the less the driver of the cutting machine will be tempted to make a deep cut which harvests soil particles too.

Resistance to diseases makes measures to prevent or to check damaging attacks less necessary or even superfluous. Thus when resistant varieties are grown production costs for the same yield are lower. In commercial production only one fungus, *Septoria digitalis* (Fig. 5a), produces damage sufficient to require chemical control. In comparative trials the fresh leaf yield of the very susceptible original accession was reduced by as much as 20% between mid-September and the end of October when chemical control was not used (Fig. 5b). Spraying twice during the growing season costs about £125 per hectare. Selection of plants which have a high degree of natural resistance to disease has produced a variety which does not need to be sprayed with fungicides.

Resistance to bolting is important because it saves labour. Plants that develop stems with flowers and fruits in the first year are called bolters. Because the leaves contain much more digoxin than other parts of the plant, the raw material for extraction should consist of leaves only. Growers should undertake to remove bolters from their crops. This can only be done



Fig. 2 Mechanised harvest of leaf crop in commercial cultivation.

by hand. Thus they prefer to cultivate a variety which does not have a tendency to bolt. Bolting is stimulated by exposure of the young plants to low temperatures. This encourages the plants to develop flowers. The amount of stimulation required to initiate bolting depends on the plant's natural resistance to bolting. Selection for this feature is not difficult. When seeds are sown in cold frames in the first days of April and the seedlings are transplanted at the beginning of June the percentage of plants that bolt (Fig. 6) is much higher than that found in field crops and in comparative yield trials which are normally drilled around the middle of April. The exclusion from further selection of all bolting plants, including those in which bolting is only incipient, has produced a high level of resistance to bolting in only a few years.

THE DRYING FACTORIES

An upright leaf attitude produces a cleaner crop.

Dry matter content—The cost of drying the leaves by means of natural gas is high. The mean dry matter content of the leaves is about 20%, and the moisture

content has to be brought down from 80% (or more if the product has been washed) to 8–10%. An increased dry matter content reduces the cost of drying. There is genetic variation in dry matter content between individual plants and their seed progenies, but non-genetic variation between individual plants caused by external conditions may also be large. This makes effective selection for this character rather difficult. Nevertheless, plants with a higher dry matter content have been selected. It is difficult, however, to combine a high dry matter content with a high yield of fresh leaves and a compromise is necessary.

THE PHARMACEUTICAL INDUSTRY

Digoxin content influences production costs. As long as the price of the raw materials is not related to its digoxin content, the pharmaceutical industry will benefit from an increased digoxin content. A decrease in the content of compounds that resemble digoxin (63 glycosides have been found in *D. lanata*) would also simplify purification. To select for a higher digoxin content individual plants are assessed

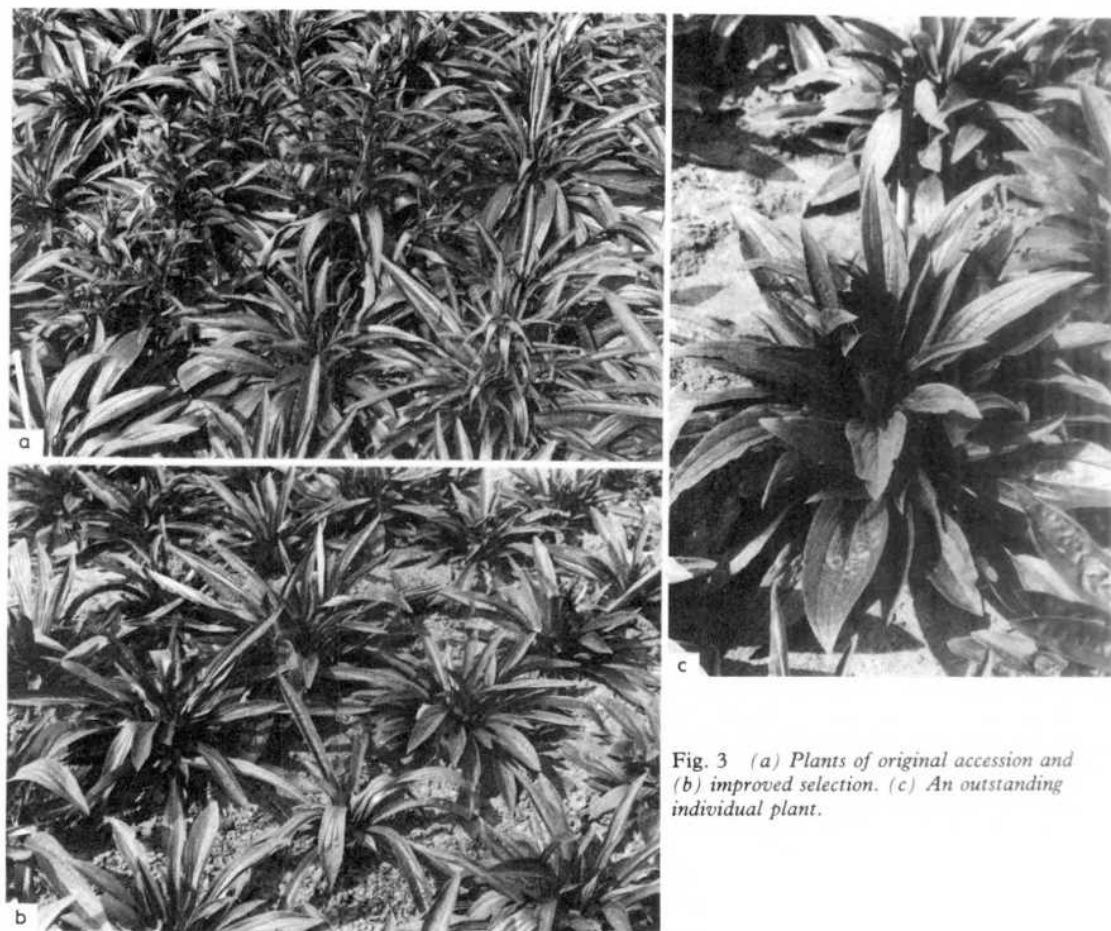


Fig. 3 (a) Plants of original accession and (b) improved selection. (c) An outstanding individual plant.

by paper chromatography. This is not a reliable method, but it is quick, simple, and cheap; and this is important since several hundred plants have to be tested in two to three weeks. In recent years samples of selections in yield trials have been investigated by high performance thin layer chromatography (Fig. 7). The digoxin content of dried leaves of the variety now in cultivation is around 2.5–3.0 parts per thousand, which is about 50% higher than the content of the original accession.

BREEDING PROCEDURE

Year 1—Selection of individual plants in spaced stands for characteristics described above in a nursery under heavy *Septoria* pressure. Only about 20 out of 10 000 plants are retained for further testing.

Year 2—Seeds are harvested from individual se-

lected plants.

Year 3—Seed progenies are tested for relevant characteristics in comparative yield trials (Fig. 8) in two replicate plots on clay and sandy soil. About 10 of the better progenies are retained.

Year 4—Repeated testing of 10 progenies as in year three. If one or two perform better than the standard over the two years, they are retained.

Year 5—Retained selections are sown for seed production.

Year 6—Seed production.

Year 7—Testing of seed progenies as in years 2 and 3 but on more plots and at different harvest dates. If only one selection performs satisfactorily, it will be used in commercial production from *Year 8* onwards, after which further seed multiplication will take place.

A new selection cycle is initiated each year, starting from progenies that are outstanding overall or for particular characteristics.



Fig. 4 Recumbent leaves remain after harvesting.

Seed production

D. lanata is self-fertile. The pollen is sticky, and selfing can be achieved by moving a small soft brush around inside the flowers. Flowers which have been treated in this way must be covered (bagged) to exclude bees and thus prevent cross pollination.

In the breeding work that I describe, however, the plants are not bagged. Bees are allowed to cross pollinate selected plants retained from year 1 for seed production in year 2. Plants with particular characteristics are grown in isolated plots to prevent cross pollination between groups. Seed production in year 6 and in successive years also takes place in isolated plots and fields.

Large numbers of bees are attracted by the glistening droplets of nectar at the bottom of the flower (Fig. 9). When the crop is in bloom bees carry the sticky pollen from plant to plant. This cross pollination produces heterogeneous progenies, and progeny produced by cross pollination of an outstanding plant is as a rule less outstanding than the mother-

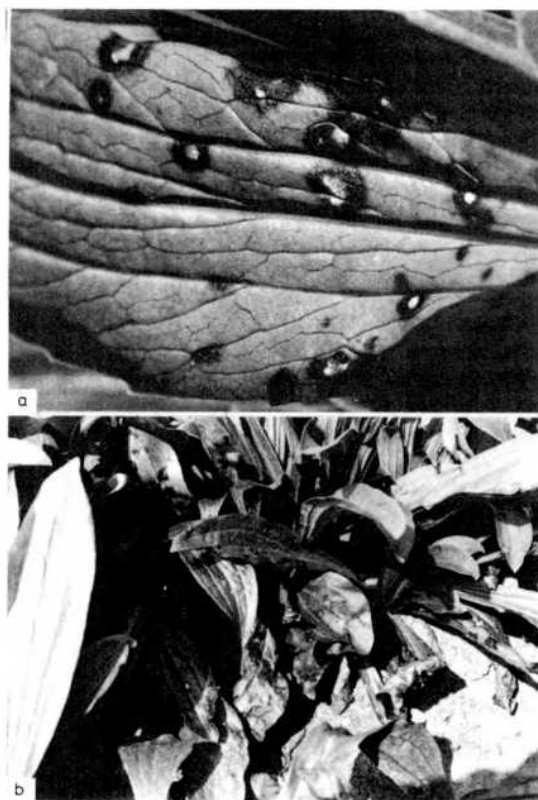


Fig. 5 (a) Leaf spot disease caused by *Septoria digitalis* and (b) heavy damage in a susceptible variety.

plant itself. The genetic contamination of outstanding plants can be prevented by raising several consecutive generations by selfing, but inbreeding depression may result. This has not so far been investigated.

Natural pollination by bees certainly brings about a high degree of inadvertent crossing between outstanding plants in year 2. Some of the heterogeneous plants produced may have new and favourable combinations of genes. Such outstanding individuals can be selected in year 1 of each new selection cycle. The very best plants may be outstanding simply because they are cross bred. If this is true, it follows that genetic segregation in the sexual progenies is unavoidable and that some genetic deterioration will take place. This may indicate that selection should continue to maintain the favourable inherited characteristics of the variety. Investigations into this question have been started, but it will take several years before a conclusion can be drawn.

Seed production may be damaged by the grey mould *Botrytis cinerea*, a widely distributed fungus,



Fig. 6 Bolting plants flower in the first year.

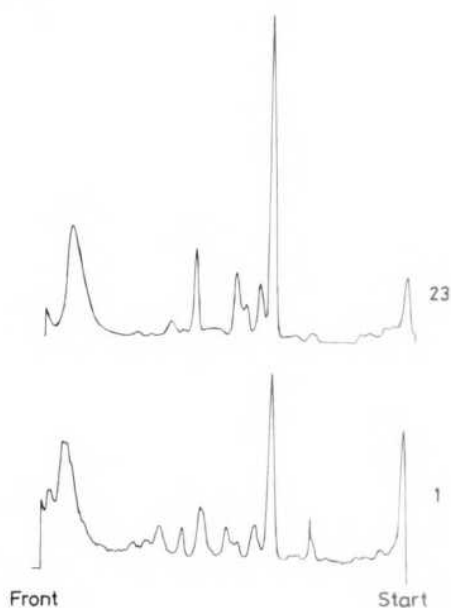


Fig. 7 High performance thin layer chromatography densitograms showing a high peak in 23 digoxin in a selected variety and in the standard 1 (TNO, Zeist, The Netherlands).



Fig. 8 Comparative yield trial.



Fig. 9 Bees bring about cross pollination.

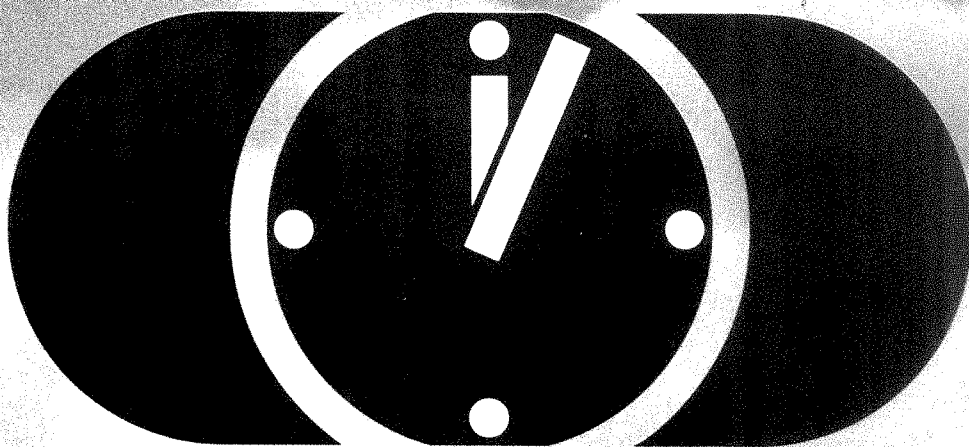


Fig. 10 A healthy stem with fruits producing many seeds (left) and a Botrytis-diseased stem producing no seed (right).

which can attack the inflorescence of *D. lanata*. In severe cases almost all the seed is lost. The fungus is only weakly pathogenic, but starting from dead flowers that remain stuck in the hairs on top of the young fruits or in the leaf axils, it may invade the stems. Growth of the fungus within the stem (Fig. 10) causes all the seed in an attacked inflorescence to be lost. The attack is favoured by rain, high air hu-

midity, and several days of high temperatures. *D. lanata* has no natural resistance to this disease, but Ronilan (vinchlozoline) which was developed to control the fungus in french beans is very effective in *D. lanata* if it is sprayed once a week (or twice a week when conditions are moist and warm) during the 6–8 week flowering period and once or twice after flowering.

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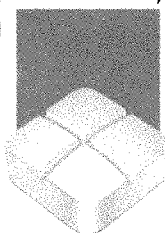
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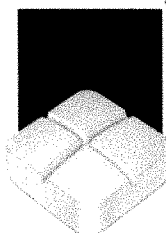
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Left ventricular aneurysm *The Wessex experience*

DANIEL J M KEENAN, JAMES L MONRO, J KEITH ROSS, JOHN M MANNERS,
NEVILLE CONWAY, ALAN M JOHNSON

From the Wessex Regional Cardiothoracic Centre, Southampton General Hospital, Southampton

SUMMARY One hundred patients with left ventricular aneurysms were operated on between February 1973 and January 1983. The principal indications for operation were left ventricular failure in 58, angina in 23, both in 17, with arrhythmia and systemic emboli accounting for one case each. Eighty five had had anterior infarction causing 82 anteroapical and three lateral aneurysms, while the remainder had had inferior infarcts resulting in 14 inferior aneurysms and one lateral aneurysm. Coronary angiography detected a single coronary lesion in 46%. Three patients had aneurysmal plication and the remainder had aneurysmectomy. Eleven mitral valve replacements were performed. Forty patients underwent coronary artery bypass grafting with a mean number of grafts per patient of 1.4. The early mortality was 7% with no early deaths since 1978. The actuarial five year survival was 68%, and 82% of survivors are in New York Heart Association class I or II (mean follow up three years). Left ventricular aneurysmectomy may be performed with a low operative mortality and good long term results.

Since 1958 when Cooley *et al* first excised a left ventricular aneurysm using temporary cardiopulmonary bypass,¹ excision of the aneurysm and removal of all thrombus has become a standard procedure.² An acquired ventricular septal defect may be closed and mitral valve surgery may be performed at the same time. Coronary artery bypass grafting is now performed on all significantly stenosed arteries that will not be excised with the aneurysm. Operative mortality has varied between 0% and 18%³⁻⁵ and is generally considered to be related primarily to the function of the residual myocardium.⁶ We reported our results in the first 20 patients in 1976,⁷ and we now analyse our experience in 100 patients.

Patients and methods

Between February 1973 and January 1983, 100 patients (83 men, 17 women; mean age 56 years) underwent repair of a left ventricular aneurysm, which was defined as a non-contractile left ventricular segment that protrudes beyond the normal end systolic and end diastolic outline of the left ventricle as

determined by left ventriculography.⁵ Myocardial infarction (83 anterolateral, two lateral, 15 inferior) had occurred a mean of 14 (SD 18) months before operation, and 11 patients had had multiple previous infarcts. The principal indications for operation were left ventricular failure alone (58), angina alone (23), and the combination of dyspnoea and angina (17). Ventricular arrhythmias were present in 10 patients, although this was the principal indication for operation in only one. Recurrent systemic embolism was present in six, but was the sole indication for operation in only one. Sixty six of those with dyspnoea were in New York Heart Association class IV with 43 of these receiving maximal medical treatment (at least 250 mg frusemide daily, digoxin, and afterload reduction).

All were investigated by left ventriculography in two planes and coronary angiography. Left ventricular end diastolic pressure was routinely measured and had a mean of 19.5 (SD 9.6) mm Hg. At angiography, 82 of the aneurysms were anteroapical, 14 were inferior, and four were lateral. Residual ventricular function was graded by examination of the left ventriculogram into good (42), moderate (44), or poor (14). Patients with globally poor left ventricular function are not included in this series.

The results of coronary angiography were available for analysis in 96 patients (Fig. 1). Eighty four had

Requests for reprints to Mr James L. Monro, FRCS, The Wessex Regional Cardiothoracic Centre, Southampton General Hospital, Shirley, Southampton SO9 4XY.

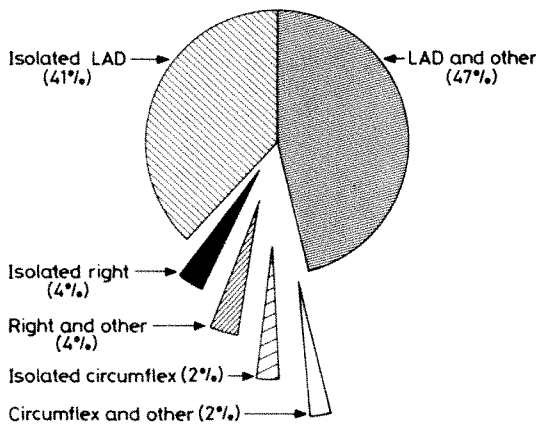


Fig. 1 Results of coronary angiography in 96 patients. LAD, left anterior descending coronary artery.

occlusion or a major stenosis of the left anterior descending coronary artery. In 39 of these patients there were no other lesions, but in the other 45 patients there were significant stenoses in other coronary arteries. In the remaining 12 patients who did not have lesions of the left anterior descending coronary artery the right and circumflex coronary arteries were equally involved. Patients were not excluded if their coronary artery lesions could not be revascularised.

Mitral regurgitation was assessed both clinically and angiographically and it was present in 37 (39%) of the 94 patients for whom data were available. It was graded as severe (6%), moderate (15%), and mild (18%). Fourteen patients had an acquired ventricular septal defect associated with the aneurysm, which was anterior in seven and inferior in seven. These were all repaired at aneurysmectomy. Aneurysmectomy had to be performed within one month of infarction on 10 occasions, and in eight of these there was an acquired ventricular septal defect. Two of these eight accounted for the only deaths in this group of very ill patients.

Operative details

Anaesthetic and cardiopulmonary bypass technique with a bloodless prime⁸ was similar in all cases. Operations performed since January 1978 have been done with cardioplegia and hypothermic perfusion.⁹ Intermittent cross clamping had been used before 1978. Three patients operated on early in the series had plication of the aneurysm whereas the remainder had an aneurysmectomy. This involved excision of aneurysmal tissue that left only a rim of fibrous tissue. The defect was repaired with two layers of a non-absorbable suture over large strips of Teflon felt. If a coronary artery bypass graft was to be performed, this

was done after excision of the aneurysm but before closure of the left ventricle. In this series a total of 56 coronary artery grafts was performed on 40 patients (Fig. 2). It was our policy to graft any stenosed major artery supplying an area not to be excised. Eleven mitral valves were replaced with Björk Shiley prostheses, most (9) replacements were performed through the ventriculotomy—which avoided opening the left atrium. It was not possible to repair the mitral valve in any of our patients. Five patients required tricuspid annuloplasty and the left atrium was opened in a further patient to achieve a complete evacuation of clot from the heart. Acquired ventricular septal defects were repaired with a Dacron patch or Teflon felt.

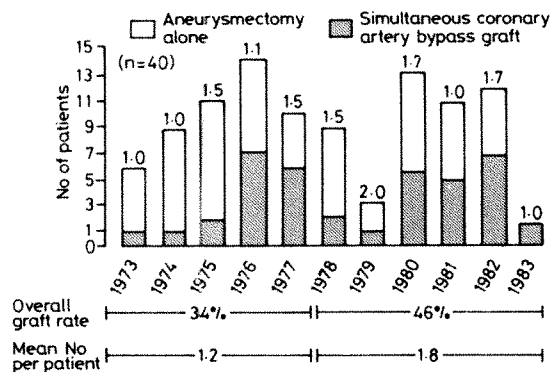


Fig. 2 Temporal relation of operations performed. (Number on top of box is number of grafts performed per patient. Average number of grafts per patient was 1.4.)

Results

Seven patients died within 30 days of operation. In one cardiac output became low at operation and this patient could not be weaned off cardiopulmonary bypass. Four died in the early postoperative period of congestive cardiac failure. At necropsy two cases showed evidence of a perioperative myocardial infarct and the remaining two deaths were caused by sudden arrhythmias. All of those who died within this period had moderate or poor left ventricular function and most had been shown to have multiple vessel coronary artery disease.

Inotropic support was required in 46 patients for at least 24 hours and the intra-aortic balloon pump was used postoperatively in nine. Five patients had prolonged left heart failure which responded to medical treatment and one required a permanent pacemaker because of complete heart block. Ventricular arrhythmias occurred postoperatively in 11 patients including the two who died of this cause. Twenty one had supraventricular tachycardia during this time. In

eight patients there was postoperative neurological impairment. This was transient in six. There was one instance of acute renal failure, which responded to conservative measures.

Late mortality was studied by the actuarial method¹⁰ (Fig. 3). Sixty eight per cent of patients were alive at five years and 57% at seven. Actuarial survival was analysed for the different main presenting symptoms. These were dyspnoea alone, angina alone, and dyspnoea with angina (Fig. 3b). Long term survival was much better in those presenting with angina alone. Analysis based on preoperative left ventricular function (Fig. 3c) showed that those with good function had an improved chance of survival, with 79% alive at five years compared with only 50% of those with poor function.

At five years 70% of those with single vessel disease were alive compared with 65% of those with multiple vessel disease (Fig. 3d). At five years 69% of those with coronary artery bypass grafts were alive compared with 66% of those without. Neither of these differences is statistically significant. Most late deaths were caused by progressive ischaemic heart disease; in many patients this was heart failure and in some there was good clinical evidence of further myocardial infarction. At review 1-11 years postoperatively

(mean three years) 82% of the survivors were in New York Heart Association classes I and II (Table). In sharp contrast to the survival statistics, there was no significant association between poor preoperative residual ventricular function and poor postoperative functional result. Six patients had postoperative cardiac catheterisation, most for persistent angina. In all of these the suture line in the ventricle was represented by an akinetic area. In two patients false aneurysms developed at the site of the suture line as a late complication and these required reoperation.

New York Heart Association classification at review, on average 36 months postoperatively.

	New York Association classification			
	I	II	III	IV
No (%) of patients	27 (36)	34 (46)	11 (15)	2 (3)

Discussion

Left ventricular aneurysms may be expected to develop in at least 10% of those who survive large myocardial infarcts. The symptoms they give rise to vary according to size of the aneurysm and to the

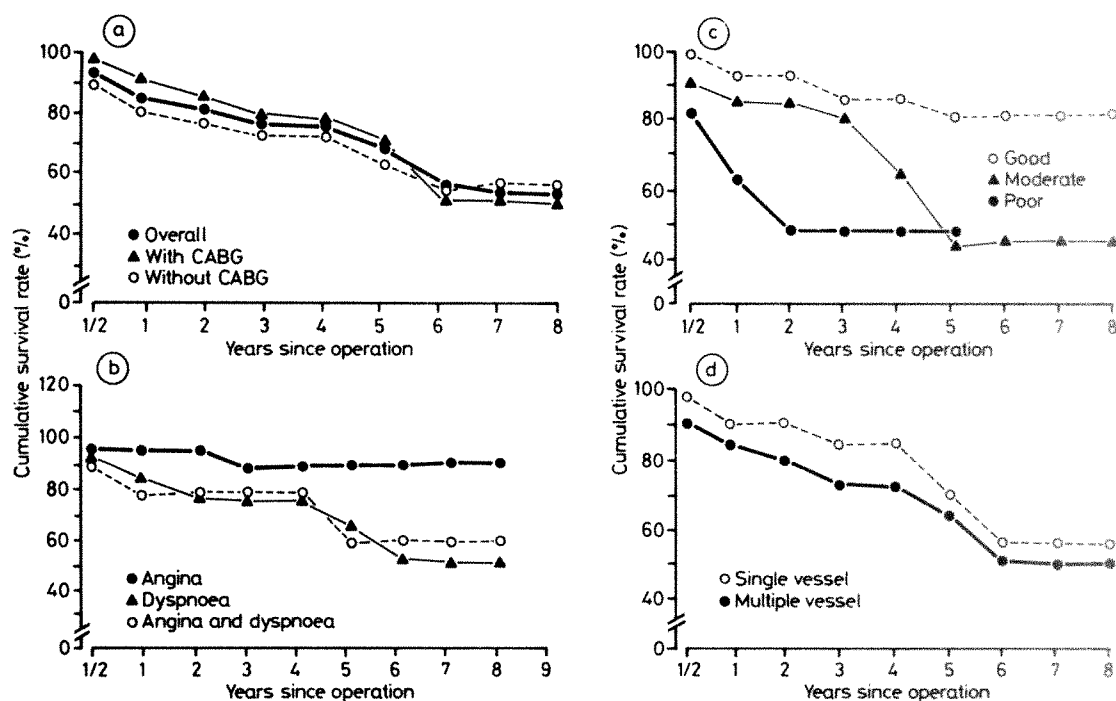


Fig. 3 Actuarial analysis of survival (a) showing influence of coronary artery bypass grafting (CABG), (b) according to preoperative symptoms, (c) according to preoperative residual left ventricular function, and (d) according to extent of coronary artery disease.

presence or absence of other major mechanical consequences of infarction (mitral regurgitation, ventricular septal defect), but the common presentation is one of congestive cardiac failure and this was so in our series. In these circumstances congestive heart failure suggests the possibility of aneurysm, and the diagnosis may be confirmed by echocardiography and left ventricular angiography. The plain chest radiograph is often misleading but can on occasion be diagnostic. Left ventricular aneurysms without symptoms have a good prognosis¹¹ and potentially a survival rate as good as 90% at five years. The outlook in patients with symptoms who are not surgically treated is poor ($\leq 50\%$ survival at five years¹¹), but with surgery life expectancy in this group is significantly improved, as others have reported.^{2,5,12} Successful surgery also results in important symptomatic improvement (Table). The selection of patients for surgery is based on the functional state of the left ventricle and the potential ventricular cavity size once the aneurysm has been resected. Both may be very difficult to judge and the argument that a ventricle able to sustain life with an aneurysm should be able to do so better without it is not necessarily valid. In our series all seven patients who died soon after operation did so because their residual left ventricular function was inadequate, and we believe that the fact that there has been no early postoperative death in the past six years reflects careful case selection as much as improvement in technique and management. This low operative mortality (7%) is in keeping with the results from other recently reported series.^{2,5,13}

Because left ventricular aneurysm is commonly caused by proximal occlusion of a single major coronary artery attention is naturally directed to the state of the other coronary arteries, which, all workers agree, should be assessed by angiography. It has been our policy, in all except the earlier cases reported in this series, to graft all arteries with significant stenoses that supply areas of myocardium not affected by the aneurysmectomy and the subsequent suture line. This practice has not increased the operative risk; our experience is the same as that reported by the Texas Heart Institute² and the Cleveland Clinic⁶ and we intend to continue this policy. The effect of bypass grafting on longer survival after aneurysmectomy is difficult to assess. Actuarial survival curves for those with single and those with multiple vessel disease in our series are similar (Fig. 3d). Also, there is no difference in actuarial survival between those who had and those who did not have coronary artery grafts (Fig. 3a). Here, one possible interpretation is that grafting converted those in whom the prognosis was worse because of multiple vessel disease into the same risk category as those in whom a single artery only was blocked. The suggestion that an aggressive approach to coronary grafting at aneurysmectomy is rewarded by longer survival¹⁴ has yet to be proved conclusively. Although only half our patients had multiple vessel

disease compared with a much higher proportion (75%) in recent series reported from the United States,^{2,5} throughout our own series the number of patients having coronary artery grafts and the number of grafts in the individual patient have tended to increase. It remains to be seen whether this trend continues.

In conclusion, despite the fact that haemodynamic measurements may show little improvement post-operatively, we believe that left ventricular aneurysmectomy should be recommended in patients with symptoms, provided that remaining left ventricular function is judged to be adequate. Coronary artery bypass grafting should be carried out at the same time for all seriously narrowed vessels supplying viable muscle. These conclusions are based on the demonstrable symptomatic improvement and improved life expectancy which have been observed after surgery for this type of coronary heart disease.

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Valvar prosthetic dysfunction

Localisation and evaluation of the dysfunction using the Doppler technique

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SUMMARY Thirty patients with 33 mitral or aortic prostheses or both were examined using the pulsed Doppler technique combined with cross sectional echocardiography to study the applicability of the Doppler technique in the diagnosis and evaluation of the severity of prosthetic dysfunction and to assess the ability of the mapping procedure to estimate the site and the size of the prosthetic defect. The dysfunction was valvar regurgitation in 29 instances and stenoses in eight, all of which were confirmed by invasive procedures. The severity of the dysfunction was graded on a three point scale. A control group of 73 subjects with 88 normal prostheses also underwent pulsed Doppler and cross sectional echocardiography. The pulsed Doppler study followed the usual procedure for a valvar disease including two and three dimensional mapping for regurgitation. Eight patients also underwent a continuous wave Doppler examination.

The diagnostic reliability of the pulsed Doppler technique was $\geq 90\%$. The severity of the dysfunction was accurately assessed in 86% of cases. In the case of aortic regurgitation, mapping of the jets was performed as easily for prostheses as for native regurgitant valves. In the case of mitral regurgitation, the mapping patterns depended on the cause of the dysfunction. With valvar tears, a jet was detected at the centre of the annulus, and with paravalvar leaks eccentric atrial jets were seen opposite the site of the leak.

The pulsed Doppler and the surgical findings correlated well for both the site of the dysfunction (16/20 (80%) patients) and the size of the leak (13/16 (81%) patients).

Thus, despite some limitations, pulsed Doppler and particularly the mapping procedure provide sufficient information to give an accurate non-invasive assessment of prosthetic valve dysfunction.

The detection of prosthetic dysfunction is incomplete with the usual non-invasive techniques.¹ The limitations of echocardiography in examining bioprostheses are fewer than with mechanical prostheses,^{2,3} and echocardiography may be helpful in detecting left atrial thrombi⁴ or abnormal kinetics.⁵ Nevertheless, the results of echocardiography may be ambiguous in a number of cases. Phonocardiography is sensitive⁶ but does not provide any information on the extent of the dysfunction or its site. With the Doppler technique, Holen and Nitter

Hauge have shown that the transprosthetic atrio-ventricular gradient may be measured using the continuous wave Doppler technique,⁷ and a few isolated cases of dysfunction have been reported using the pulsed or continuous wave Doppler technique.^{8,9} In addition, the pulsed Doppler technique makes it possible to grade the severity of the acquired valvar defect on the basis of velocity patterns^{8,10,11} or indices of severity.¹²⁻¹⁴ Moreover, the mapping procedure helps in identifying the site of the dysfunction. We applied this technique to determining the severity of the prosthetic dysfunction and to identifying its site.

Patients and methods

The study population consisted of 30 patients (14

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Table 1 *Types of prostheses investigated with the Doppler technique*

Type of prosthesis	Malfunctioning prostheses	Normal prostheses
Aortic.		
Starr-Edwards	7	19
Bjork	3	4
Bioprostheses	3	11
St Jude	1	1
Miscellaneous		3
Total	14	38
Mitral.		
Starr-Edwards	6	31
Bjork	3	5
Bioprostheses	9	6
Gabbar Meadox	1	2
Miscellaneous		2
Total	19	46
Tricuspid.		
Starr-Edwards		3
Pulmonary.		
Bioprostheses		1
Total	33	88

women and 16 men, mean age 48 years) with 33 malfunctioning prostheses (Table 1), in whom the prosthetic dysfunction was diagnosed by invasive procedures including left heart catheterisation with left ventricular cineangiograms or aortic root angiograms or both (21 cases), or surgery (21 cases), or at necropsy (one case). The dysfunction was valvar regurgitation or obstruction, or both (37 instances, involving 38 causes since regurgitation was due to both a paravalvar leak and a valvar tear in one patient). Table 2 shows the cause of the dysfunction identified at surgery or necropsy. Twenty patients were in sinus rhythm and six in atrial fibrillation; three had implanted pacemakers and one incomplete atrioventricular block.

A control group of 73 patients (38 women and 35 men, mean age 54 years) were examined at the same time. They had 88 normally functioning prostheses (Table 1) on the basis of no cardiac symptoms

Table 2 *Type of prosthetic defects causing regurgitation or obstruction. Figures are number of defects*

	Mitral valve	Aortic valve
Regurgitation		
Paravalvular leak		
Primary	5	2
Secondary to endocarditis	4	5
Valvar lesion on bioprosthesis		
Primary	2	
Secondary to endocarditis	2	1
Unknown origin*	5	4
Obstruction		
Endocarditis vegetations	1	
Thrombus		2
Fibrosis or calcifications	1	1
Unknown origin*	3	
Total	23	15

*Patients who did not undergo repeat surgery.

detected at clinical examination or by phonocardiography and echocardiography. In 10 controls with transient equivocal clinical data a later invasive study failed to detect a prosthetic dysfunction.

CLASSIFICATION OF THE DYSFUNCTION

For patients who had undergone angiography the severity of the dysfunction was graded as mild, moderate, or severe.¹¹⁻¹³ For patients who had undergone repeat surgery the classification was based on the presence of vegetations, thrombosis or fibrosis or both, calcification (in the case of obstruction), valvar perforation (in the case of bioprostheses), and the extent of the annular leak in relation to the whole circumference of the prosthesis (mild, disruption of a few points; moderate, disruption equal to a quarter of the circumference; severe, disruption equal to a third of the circumference). The same classification was used for the findings at necropsy.

DOPPLER ECHOCARDIOGRAPHY

We used a 3 MHz ATL 851 (Squibb Medical System, Bellevue, Washington, USA) mechanical real time scanner, which provided a 90° sector and single gate steerable pulsed Doppler capability. The Doppler output could be presented as an audible signal, a time interval histogram, an analogue flow velocity trace, and a real time frequency spectrum by means of a fast Fourier transform analyser (Angioscan) (Unigon Industries, Mount Vernon, New York, USA). The principles and characteristics of the instruments have been described elsewhere.¹⁵⁻¹⁷

For eight patients and 22 controls we also used a 2.5 MHz continuous wave Doppler SONACOLOR CD (Carolina Medical Electronics, King, NC, USA). This instrument shows the positive or negative Doppler shifts from the zero reference to 20 KHz since the polarity may be switched. Real time spectral analysis is performed every 10 ms over a selectable frequency range to provide the equivalent of 256 band pass filters spaced at 100 Hz intervals.¹⁸ A thermal colour coded scale from red (weak signal) to white (strong signal) indicates the amplitudes within the spectrum. Audiosignals are also simultaneously fed to stereo speakers. The pulsed Doppler signal may also be fed to the instrument for real time spectral analysis.¹⁹ One recording was made using a 2 MHz continuous wave instrument (Alfred) (Pedof, Vingmed A/S, Norway).

The procedures used for investigating prostheses with pulsed Doppler are similar to those already described for left sided valvar defects.²⁰ For aortic prostheses, we recorded the aortic velocity traces from the suprasternal notch and in the left parasternal long and short axis views (at aortic and left

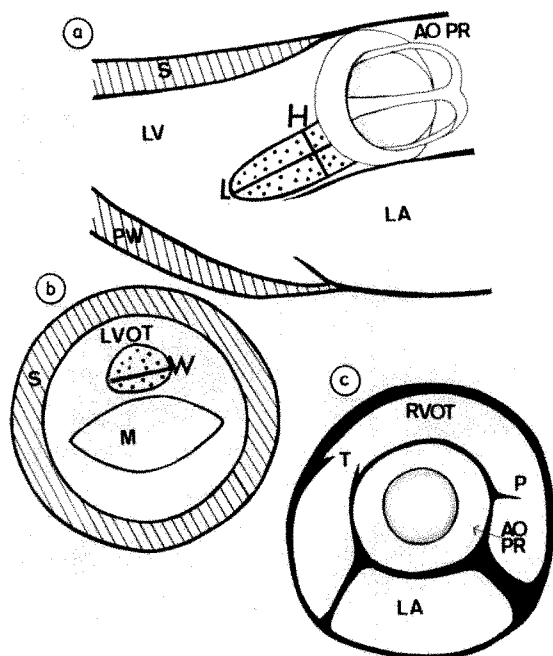


Fig. 1 Diagrams showing the calculation of the left ventricle outflow tract regurgitant index for assessing the severity of aortic regurgitation in a prosthetic aortic valve: the product of the length (L) and height (H) of the disturbed area in relation to the regurgitant flow (dotted areas) in the parasternal long axis view (a) and of its width (W) in the parasternal transverse aorta short axis view (b) equals the left ventricle outflow tract regurgitant index. (c) Shows the entire aortic prosthesis in the transverse aorta short axis view for the diagnosis and evaluation of both stenosis and regurgitation (regurgitant aortic valvar area). S, septum; R or LVOT, right or left ventricle outflow tract; LA, left atrium; M, mitral valve; T, tricuspid valve; P, pulmonary valve; PW, posterior wall; AO PR, aortic prosthesis; L, H, W, length, height, and width of the disturbed area in centimetres.

ventricular levels) (Fig. 1). For mitral prostheses (Fig. 2), we recorded the traces in (a) the long axis parasternal view using, if necessary, the manoeuvre recommended by Nishimura *et al*²¹ in order to transect the prosthetic annulus in more than one longitudinal plane, (b) the short axis plane, paying particular attention to the intermediary plane between the level of the aortic and mitral orifices, in order to scan the anterior part of the prosthetic ring, and (c) the four chamber view and, more rarely, the subcostal approach.

When the continuous wave mode is used the angle θ between flow and the ultrasonic beam should be reduced as much as possible so we generally sited the probe in the suprasternal notch for aortic prostheses and at the apex of the heart for mitral prostheses.^{22 23}

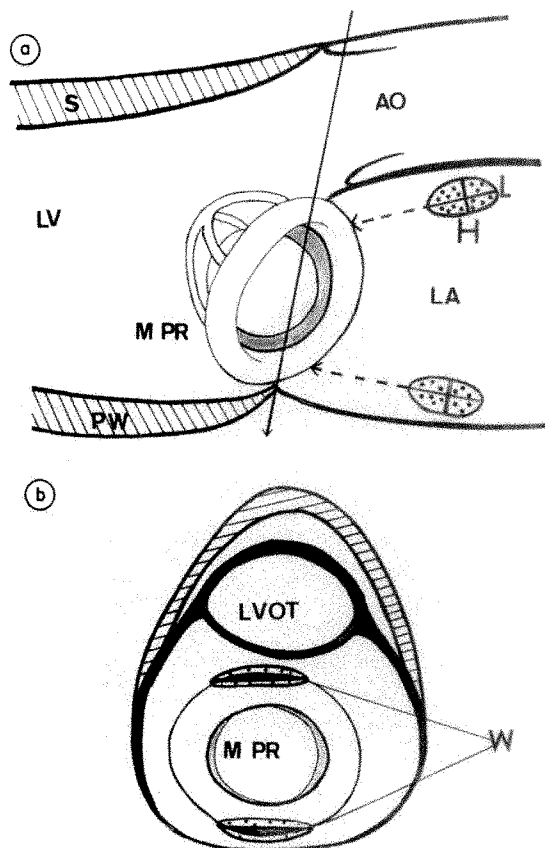


Fig. 2 Diagrams showing the calculation of the total regurgitant index in assessing the severity of mitral regurgitation in a mitral prosthesis. In (a) the length and height of the disturbed area in relation to the regurgitant flow (dotted area) are measured and the long axis regurgitant index calculated as $1/2 L \times H$. When the disturbed area is not followed from the centre of the prosthesis the length is considered to be equal to the distance of the farthest atrial disturbance from the plane of the annular prosthesis (dotted line). In (a) the prosthesis is drawn in perspective, whereas in (b) the heart is transected along a single plane. The oblique line in (a) transecting the left cavities corresponds to the level of the short axis plane used in (b) for the measurement of the width (W) of the regurgitant flow, which is the short axis regurgitant index. The total regurgitant index is equal to $(1/2 L \times H) \times W$. The apical four chamber view usually used to record the mitral flow velocity traces is not shown. (AO, aorta; MPR, mitral prosthesis; for other abbreviations see Fig. 1).

VARIABLES STUDIED

Pulsed Doppler—The aortic and mitral velocity traces were examined for both the presence or the absence of systolic or diastolic disturbances in all patients.^{8 10 11} In addition, we localised areas of

abnormal spectral display; in cases of regurgitation we localised the regurgitant jet in the left ventricular outflow tract for aortic prostheses and in the left atrium for mitral prostheses. We used the same criteria for the definition of an abnormal spectral display and the same techniques for mapping and measuring areas or jets or both and for calculating indices of severity as those previously reported.¹²⁻¹⁴ These calculations are schematically illustrated in Figs. 1 and 2. In cases of mitral regurgitation, when an area

of systolic atrial disturbance could not be followed point by point: from the atrium towards the prosthetic annulus the length of the regurgitant jet was assumed to be equal to the distance between the farthest point of disturbance and the plane of the annulus in centimetres. We also noted the site of the atrial disturbance in the four chamber view in relation to the central part of the atrium and the atrial walls.

The width of the Doppler disturbances detected in

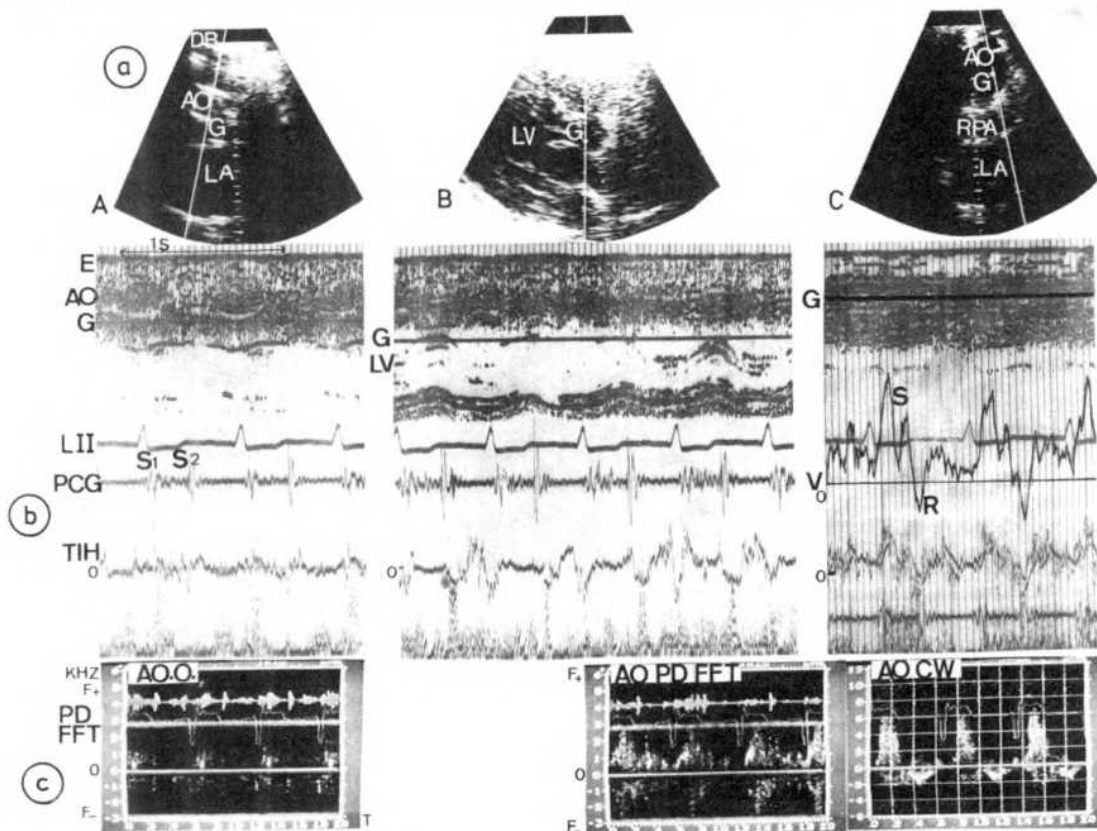


Fig. 3 (a) Cross sectional echocardiograms, (b) pulsed Doppler recordings with the signal fed to a zero crossing meter and (c) to a fast Fourier transform real time analyser (of a normal aortic prosthesis). (A) shows the transverse aorta short axis view (the Doppler beam is shown as a white line (DB) and the gate as a white spot (G) at the level of the prosthesis). (B) the parasternal long axis view (the gate is in the left ventricle outflow tract beneath the aortic valve; the spectrum consists of a line of clustered dots in both parts of the cardiac cycle), and (C) the suprasternal approach of the ascending aorta (the gate is in the aorta). (b) (left and middle panels) shows two systolic deflections related to the opening and closing of the cusp and some transient early systolic minor broadening of the spectrum, which is shown as a thin line for the remainder of the cardiac cycle. The same pattern is for the real time spectrum analysis. (b) (right panel) shows one systolic positive (S) and one transient negative in early diastole (R) with no more negativity in the remaining part of diastole. In this case, velocities reached 1.80 m/s as shown by the recording using continuous wave Doppler (c, right panel). Some segments of the venous pattern are superimposed on the arterial pattern with this equipment. DB, Doppler beam; G, gate; RPA, right pulmonary artery; LII, lead II of the electrocardiogram; PCG, phonocardiogram; S₁, S₂, first and second heart sounds; TIH, time interval histogram; V, velocity trace; O, zero line; AO O, aortic orifice; PDFFT, pulsed Doppler signal fed to a fast Fourier transform analyser, CW, continuous wave Doppler; KHZ, kilohertz; F₊, F₋, positive and negative Doppler shift; T, time axis (other abbreviations as in previous Figs).

the short axis view, representing the size of the leak, was expressed as a percentage of the circumference and compared with the surgical findings.

Continuous wave Doppler—The blood velocities were calculated on the basis of 0.30 m/s for 1 KHz Doppler shift, assuming optimal alignment between the flow and the ultrasonic beam. The half pressure time and the pressure gradient were calculated when appropriate from the simplified Bernoulli equation: $P_1 - P_2 = 4V_2^2$, according to Hatle *et al* and Holen *et al.*²³⁻²⁵

Recordings were made either on a Sony videotape recorder with hard copies of real time imaging on a 4633 Tektronics recorder, or on a Panasonic videotape, with imaging using polaroid film. Simultaneous electrocardiograms (lead II), phonocardiograms, and M mode echocardiograms were usually recorded with the pulsed Doppler display on

an IREX 101 (IREX, Mahwah, NJ, USA) multi-trace system. All recordings were performed by two independent observers and each of them reviewed the videotapes. There was no significant inter-observer and intraobserver discrepancy between the results ($r=0.95$ and 0.97). The conclusions drawn from the Doppler data were made independently from the results of the invasive procedures and were performed by separate teams.

Results

NORMAL PROSTHESES (Figs. 3 and 4)

The Doppler technique did not show any abnormality in 85 of 88 prostheses. In the remainder minor aortic (2) and mitral (1) regurgitation without any measurable jet was not confirmed by other clinical

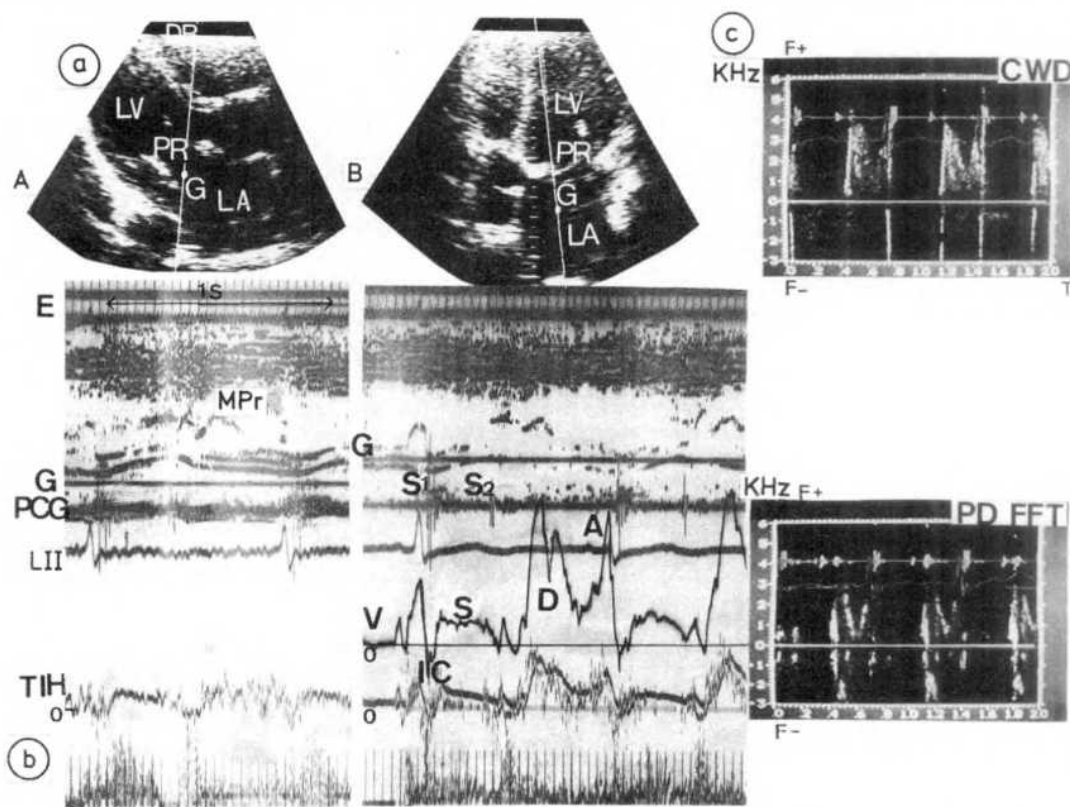


Fig. 4 (a) Cross sectional echocardiograms, (b) pulsed Doppler recordings, and (c) real time analyses of a normal mitral prosthesis. (A) shows the parasternal long axis view with the gate at the annulus (the Doppler spectrum consists of a thin line of clustered dots; the same features would be recorded at the annulus in the short axis view), (B) the apical four chamber view (the mitral flow velocity trace is recorded with its four constituents) IC due to the isometric contraction and S at or slightly above the zero line in systole and the two filling diastolic waves D and A (some frequency aliasing may be seen in early diastole, which is better shown in (c) bottom panel; (c) (top panel) shows the continuous wave Doppler trace. (Abbreviations as in previous figures.)

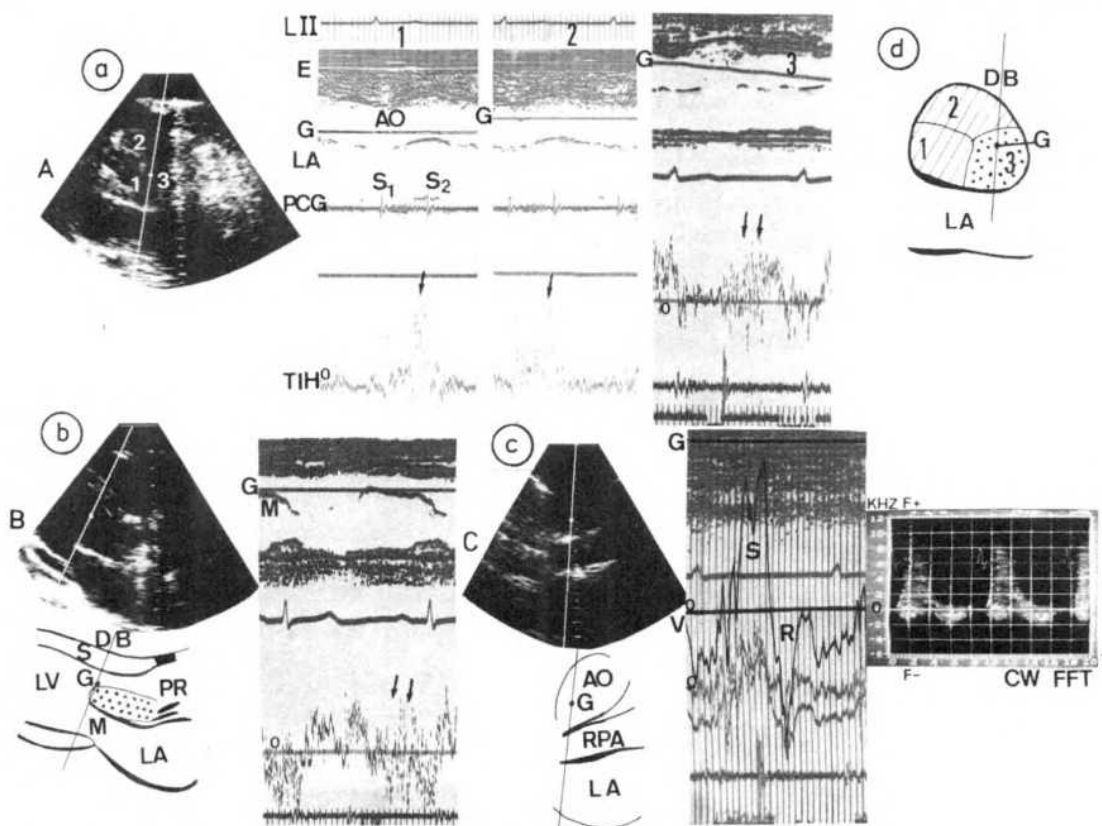


Fig. 5 Recordings (as in Figs. 3 and 4) showing severe dysfunction of a Hancock bioprosthesis with stenosis and regurgitation. (a) Shows the transverse aorta short axis view (A), (a) (middle two panels) systolic disturbance (single arrow) at the site of the non-coronary (1) and of the right coronary (2) cusps (striped areas on (d)) related to fibrosis and calcifications as confirmed at surgery and (a) (right panel) diastolic disturbance (twin arrows) at the site of the left coronary cusp (3) (dotted area on (d)) owing to destruction of this cusp by an infective process. (b) Shows the parasternal long axis view (B) (the gate is in the left ventricle) and (b) (right panel) diastolic disturbances (twin arrows, dotted area); the regurgitant index is 20 (severe regurgitation). (c) Shows the suprasternal approach of the aorta (C), and (c) (right panel) both stenosis and regurgitation. The systolic pressure gradient calculated with the continuous wave was 40 mm Hg (moderate stenosis), which agrees with the pulsed Doppler assessment of severity at the level of the aorta. (PR, prosthesis, other abbreviations as in previous figures.)

investigations; one patient later had a normal angiogram.

DYSFUNCTIONING PROSTHESES (Figs. 5-7)

The pulsed Doppler technique diagnosed 35 dysfunctions out of 37. One false negative aortic obstruction was detected at necropsy and one case of mitral regurgitation was due to a valvar tear. Three paravalvar leaks were not identified in cases of regurgitation (one mitral leak associated with a valvar tear and two aortic leaks). The sensitivity, specificity, predictive value, and accuracy were 94%, 96%, 92%, and 96% respectively. The evaluation of the severity of the dysfunction relied on the examination

of the velocity traces in nine cases, including continuous wave recordings in two cases of obstruction and on the determination of indices in 26 cases of regurgitation. There were three errors (one over and two underestimations).

No abnormalities were detected with the mapping procedure for aortic regurgitant jets. In cases of mitral regurgitation, the long axis view showed systolic disturbances at the centre of the annulus entailing a central atrial jet in the same plane and in the four chamber view in only five patients. Among the remaining patients, these disturbances were found only in the left atrium away from the annular centre. In these patients the annular detection was

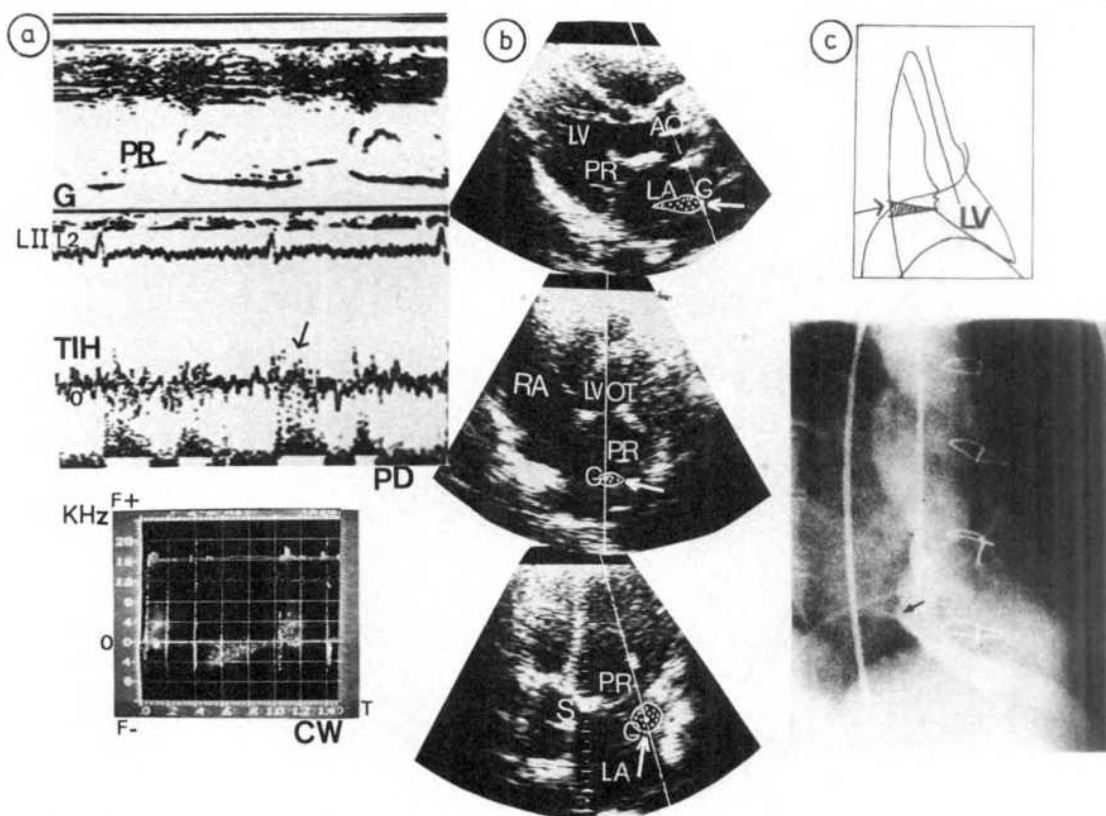


Fig. 6 (a) Pulsed Doppler recordings (top and middle panels) and continuous wave recording (bottom panel), (b) cross sectional echocardiograms, and (c) angiogram showing a paravalvar leak on a mitral Gabbay Meadox prosthesis. (a) Shows early systolic disturbance in the left atrium (arrow). The velocity of the regurgitant jet is 3 m/s as shown by the continuous wave Doppler (the Doppler shift has been artificially reversed and velocities related to the regurgitation are positive, although the probe is at the apex). (b) Shows these spectral disturbances at three sites: top, in the left atrium seen in the long axis view along the posterior wall; middle, at the centre of the posterior part of the annulus in the short axis view; bottom, below the previous attachment of the posterior leaflet in the four chamber view (dotted areas shown by white arrows). The total regurgitant index is 2.5 (mild regurgitation). (c) Shows a discrete regurgitant jet at the inferior part of the annulus. At the time of the operation, there was a 8 mm paravalvar leak at the centre of the previous area of insertion of the posterior leaflet. The patient underwent surgery because of severe haemolysis. (Abbreviations as for previous figures.)

assessed only in the short axis view. When the three approaches are combined the following Doppler features were noted for this group: five patients had posterior annular systolic disturbances in the short axis view, with some additional ones in the lower half of the atrium in the long axis view and near the external atrial wall in the four chamber view; six patients had anterior annular systolic disturbances in the short axis view, with some additional ones in the upper half of the atrium in the long axis view and towards the interatrial septum in the four chamber view.

Table 3 shows the size of the annular ring and the width of the Doppler abnormalities in 13 patients with paravalvar leaks.

The site of the dysfunction was confirmed at reoperation in 16 (80%) of 20 patients (Table 4). Paravalvar leaks were present along the previous attachment of the anterior mitral valve (three patients) and of the posterior valve (three patients), and they overrode the previous posterior (one patient) and anterior (one patient) commissures. In these two instances, Doppler detected only a posterior and an anterior site. For the aortic orifice, it was not possible to determine accurately the site of the disturbance in one patient with poor echocardiographic visualisation of the aortic annulus, although measurements could be performed. The Doppler technique detected two paravalvar leaks along the non-coronary cusp, one along the right

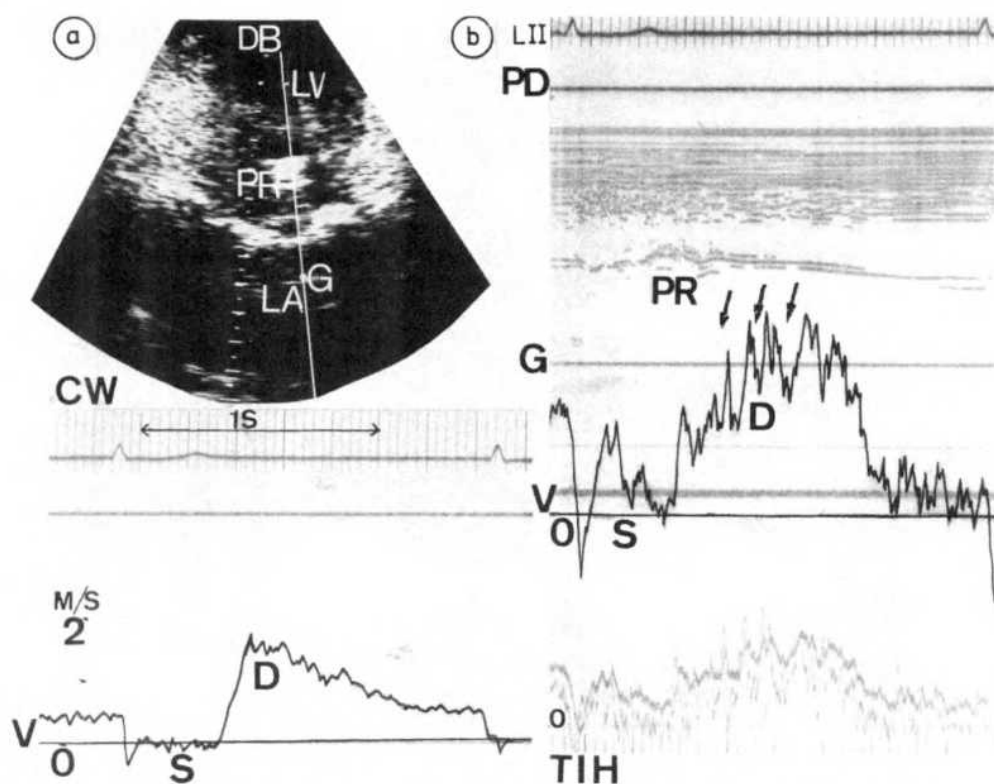


Fig. 7 Recordings (as before) of obstructive dysfunction of a mitral bioprosthesis showing pronounced diastolic abnormalities using the four chamber approach ((b) arrows). The continuous wave (CW) recording shows increased early diastolic velocities approaching 2 m/s; mean value of pressure half time is 0.27s. Surgery showed obstructive postinfective alterations and a thrombus filling the left atrium up to the annulus. (Abbreviations as in previous figures.)

coronary cusp and one overriding the previous commissure between the coronary cusps. In this patient, however, an additional minor leak along the non-coronary cusp was overlooked.

One tear of the aortic left coronary cusp and two tears on the anterior (1) and posterior (1) mitral cusps were detected by Doppler, which failed to detect posterior tear on another bioprosthesis. There

Table 3 Comparison of pulsed Doppler and surgical findings for the size of the paravalvular leak

Type of prosthesis	Ring diameter (mm) at surgery	Width of annular Doppler anomalies (mm)	Leak/circumference	
			Doppler (%)	Surgery*
Mitral:				
Björk	31	28	28	1/3
Björk	29	15	16	1/4
Starr	30	30	31	1/3
Starr	31	4	4	Minimal
Bioprosthesis	31	20	20	20 mm
Bioprosthesis	33	15	14	0-10
Bioprosthesis	31	28	28	1/3
Gabray Meadox	29	10	10	8 mm
Aortic:				
Starr	23	22	30	1/3
Starr	23	19	26	1/4
Starr	21	25	37	2 leaks (8 mm, 12 mm)
Starr	23	20	27	1/3
St Jude	25	10	12	6 mm

*Approximate size on the basis of visual inspection.

Table 4 Surgical findings confirming the site of the prosthetic dysfunction

	Aortic prostheses	Mitral prostheses
Regurgitation:		
Site of paravalvar leak	4/5	6/8
Site of valvar lesions on bioprostheses	1/1	2/3
Obstruction:		
Site	2/2	1/1

were no discrepancies in the results in the cases of obstruction.

Discussion

The difficulties encountered by non-invasive techniques in evaluating prosthetic dysfunction are often reported. Nevertheless, many limitations apply equally to the invasive procedures in the same circumstances, either because the association of two prostheses in a given patient does not allow haemodynamic studies or because repeat cardiac catheterisation is refused by patients. In our study, endocarditis was present in 14 cases, which in most cases caused regurgitation. When necessary, in view of the severity of the dysfunction, these patients underwent urgent surgery. The high incidence of dysfunctioning prostheses in our study in relation to the number of normal prostheses examined during the same period has, of course, no significance, since patients were referred to our laboratory from several hospitals for Doppler examination.

As already stated in a previous paper,²⁶ because of the technological limitations inherent in the pulsed Doppler devices, particularly the Nyquist limit, we did not take into account the absolute velocities of flow traces but only their pattern and timing anomalies. For spectral anomalies, diagnosis relied on an all or none analysis, and not on the amplitude of the spectral broadening, which was susceptible to observer bias. Recent technological improvements tend to minimise these limitations. The colour coded Doppler apparatus recently introduced, however, does not solve all the problems raised by the quantification of regurgitation on prostheses mainly because of strong reverberation echoes.²⁷ In brief, although limitations exist in the use of single gated Doppler, these should not detract from the value of the pulsed Doppler technique combined with cross sectional echocardiography.

NORMAL PROSTHESES

Postoperative invasive studies are not routinely performed in healthy subjects with prostheses. Thus only a few subjects were studied using invasive procedures; and because of this the overall specificity should be interpreted with caution. Nevertheless,

this specificity is satisfactory for this small group. The few false positive diagnoses might be accounted for by the greater sensitivity of Doppler in detecting minimal backflow on a prosthesis. The Doppler features were similar to those previously reported.^{8,9} Fig. 4 shows that frequency aliasing may be present on normal prostheses. Flow velocities are frequently higher than those across a native valve, probably because of the presence of discrete transprosthetic pressure gradients.^{28,29}

DYSFUNCTIONING PROSTHESES

The predominant dysfunction encountered in our study was valvar regurgitation. The incidence of valvar obstruction is now lower because of improvements in the new generation of prostheses and the decreased incidence of thrombosis on bioprostheses. The diagnostic reliability of Doppler in our study, which was similar to that obtained in studies of stenoses on native valves, suggests that the pulsed Doppler technique is applicable to the study of prostheses. The same applies to continuous wave Doppler, as previously reported by others.^{7,9} Nevertheless, with the latter technique, the study of the half pressure-time might be more sensitive than the increase in absolute velocities in detecting mitral obstruction since these patients often have low cardiac output. Low cardiac output is likely to be the cause of the false negative diagnosis of aortic obstruction since it produced a normal aortic velocity trace. The mapping of systolic disturbances at the aortic orifice might be more reliable but could not be performed in one patient because of unsatisfactory echocardiograms. This emphasises that one of the advantages of using pulsed Doppler is its ability to identify the site of the dysfunction. Fig. 5 shows that each cusp of a bioprosthesis may be the site of a different defect, each one requiring accurate evaluation.

Regurgitation is due to valvar tears in cases of bioprostheses and to paravalvar leaks in cases of mechanical and biological valves. In our study the mapping procedure using the long axis approach for aortic prostheses was as accurate as that used for native regurgitant valves. The diastolic disturbances were generally detected immediately below the aortic orifice, either anteriorly or posteriorly in the outflow tract depending on the site of the regurgitation. The calculation of the long axis regurgitant index caused overestimation in one patient with a mitral prosthesis and underestimation in one patient with a severely dilated ventricle. In cases of mitral regurgitation the findings differed considerably from those of native regurgitant valves. Regurgitations on native mitral valves generate central systolic disturbances at the point of the leaflet's coaptation.

From this central point the jet is mapped point by point into the atrium.¹³ Surprisingly, this mapping pattern was rarely found on prostheses. Two patients with such findings underwent repeat surgery and both had a valvar tear on a bioprosthesis. Moreover, in both there was an unusual high pitched and musical tone, as already stressed in such cases by Sabbah *et al*.³⁰ These findings might be a feature of valvar defects.

On the other hand, the features encountered in patients with paravalvar mitral leaks were characterised by eccentricity of the jet. The centre of the prosthesis was free of disturbances. In addition, the jet could not be mapped in its entirety from the annular plane to its farthest atrial point, and the disturbances, sometimes seen only in a parallel long axis plane, were found at a variable distance in the atrium, which meant that some points had to be extrapolated between the disturbed area and the annulus for measurement of the length of the jet. Some conditions might alter the features of paravalvar leaks that we observed. Figure 2 shows that the prosthetic annulus is transected by the echocardiographic plane at two opposite points where the leak may, or may not, be located. In the first instance only can the eccentric jet be mapped in its entirety. Moreover, some important leaks might entail a regurgitant flow in the central part of the atrium. None of these situations occurred in our preliminary study. The conditions entailing an eccentric jet also apply to aortic leaks, in which, however, the regurgitant jets are easily mapped. Reasons for that are unclear. Configuration and haemodynamics of the left atrium and ventricle are not similar, and the relation between chamber size and prosthesis is different. Furthermore, eccentricity of the jet increases with the diameter of the prosthesis.

With the short axis approach, the detection of the Doppler anomalies had a three fold interest. It first led to quantifying the regurgitation on the basis of a three dimensional index, as already proposed for native regurgitant valves.^{13 14} Satisfactory grading was obtained because the three dimensional approach took into account the unusual features of some jets such as wide annular jets with limited upstream spread. Furthermore, provided that the mapping was performed at the actual site of the mitral and aortic orifices, this approach identified the site of the dysfunction with the same reliability as that for native valves.^{12 13} Finally, Doppler mapping in the short axis view represented a unique ability to compare Doppler and invasive measurements. Indeed, in the case of paravalvar leaks, when the examiner measures the width of the Doppler anomalies at the prosthetic annulus he actually assesses the size of the leak. This size may be expressed as a

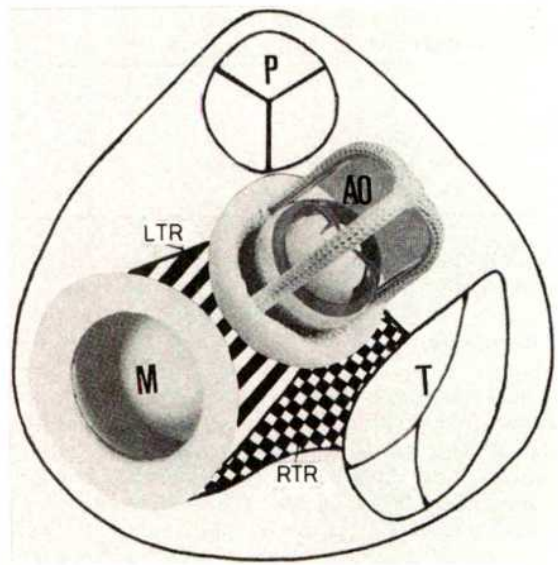


Fig.8 Diagram of the anatomical relation of the heart valves showing the base of the heart, the atria having been removed. The anterior part of the prosthetic mitral annulus corresponds to the fibrous attachment of the previous anterior mitral leaflet, which involves for its anterior two thirds the left fibrous trigone, and for its posterior one third the right fibrous trigone. These relations need to be borne in mind when identifying the site of a dysfunction in a prosthesis because they explain, for instance, the preferential atrial direction of the jets due to mitral paravalvar leaks observed during the Doppler examination. (L and R TR, left and right trigone, other abbreviations as for previous figures.)

percentage of the whole circumference, since the prosthetic diameter is known, and correlated with the surgical findings, which are often based on the same calculation. The surgical assessment did not rely on accurate measurements but rather on visual inspection. Nevertheless, Table 3 shows that the Doppler estimation of the size of the leaks agreed with that found at surgery. This also applies to the size of valvar defects. Differences in flow dynamics between the Doppler and surgical investigations might explain some discrepancies.

Furthermore, correlations with the surgical findings suggest that generally the areas of disturbed flow were almost opposite the site of the leak. For instance, regurgitation due to paravalvar leaks along the previous attachment of the anterior mitral valve spreads towards the upper atrial portion in the long axis view and towards the interatrial wall in the apical view and conversely (Fig. 6). Some inaccuracies regarding the leaks overriding the previous commissures will need further study. Some very small leaks may require repair because they cause severe dis-

turbance; sometimes they are difficult to detect at the time of operation. The use of the Doppler technique is crucial for their localisation. For this purpose, reference to standardised anatomical landmarks, such as the previous attachment of valves and commissures, is recommended to achieve better correlations. The Doppler examiner should always keep in mind the anatomical relations of the cardiac orifices, as shown in Fig. 8, when locating a defect.

LIMITATIONS OF THE METHOD

Low cardiac output, poor postoperative echocardiographic visualisation, and weak signal to noise ratio are well known factors that might produce false negative diagnoses or underestimations or both. The presence of a mitral prosthesis, mitral valve disease, or an irregular heart rhythm might make the measurement of aortic jets in the left ventricle difficult. Errors might be introduced into results when some measurements have to be extrapolated, but this was not a source of error in our study. In addition, poor lateral resolution is likely to be the cause of inaccurate measurements. Two closely associated defects causing the same disorder, such as a leak and a valvar tear, make diagnosis difficult. In one case of mitral obstruction due to prosthetic fibrosis we overlooked an additional cause, which was an atrial thrombus. The multigate Doppler technique might lead to more accurate information in such cases. Failure to map the eccentric jet in its entirety in the case of mitral leaks is, in fact, due to the inability of the present equipment to display the disturbed flows in a three dimensional frame and should be overcome in the future.

The work was partly supported by grants from CNAMTS and the ARNTIC Research Association.

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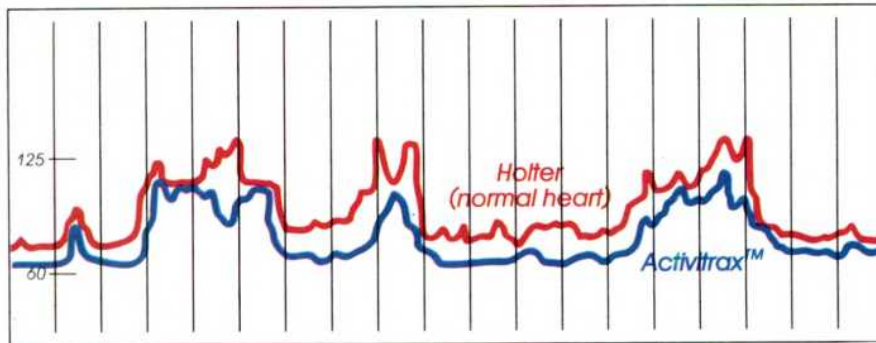
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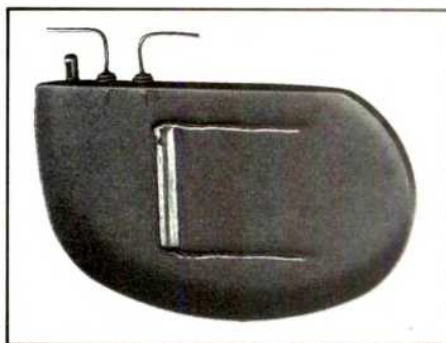
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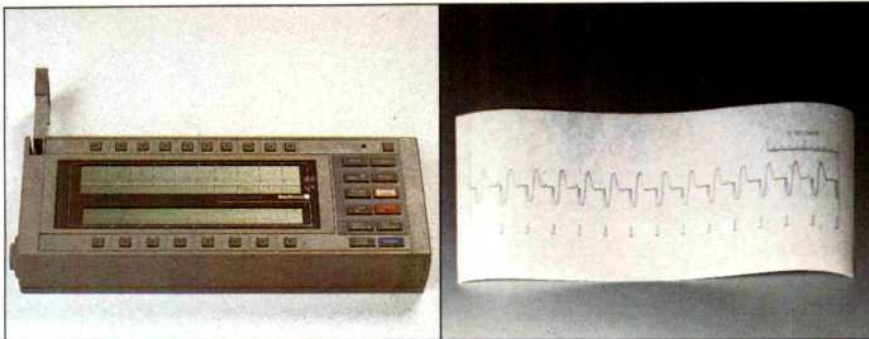
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Balloon valvuloplasty and angioplasty in congenital heart disease

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SUMMARY Balloon dilatation valvuloplasty was performed in 16 patients with pulmonary valve stenosis aged 10 days to 17 years. Gradients were reduced in all but two patients and were ≤ 20 mm Hg after the procedure in all but these two and one other. Unsatisfactory initial results in these three patients were attributed to the use of too small a balloon in one patient (gradient subsequently abolished at repeat valvuloplasty), to a dysplastic valve in a neonate, and to the fact that there had been a previous surgical valvotomy with scar tissue formation in one patient. The good result was retained in six of seven patients followed up at three to six months. In one the gradient, having been reduced from 60 to 18 mm Hg, had risen to 35 mm Hg. Repeat valvuloplasty was technically impossible in this patient, but in two others residual gradients of 24 and 22 mm Hg were reduced to 4 and 8 mm Hg respectively by repeat valvuloplasty. Balloon dilatation angioplasty was successful in dilating a severe stenosis at the lower limb of an atrial baffle (previous correction of complete transposition) and in dilating supra-valvar stenosis of the pulmonary artery resulting from previous banding and debanding.

Thus balloon pulmonary valvuloplasty, though still a new technique, appears to be the treatment of choice in patients with typical pulmonary stenosis and thin mobile valves. Patients with dysplastic valves may be less suitable candidates for the procedure. Balloon angioplasty is likely to have other applications, including the treatment of postoperative stenotic lesions.

In 1982 Kan and coworkers reported the first use of percutaneous balloon valvuloplasty for the successful treatment of a patient with pulmonary stenosis.¹ Since that time the same group has reported details of 20 patients treated in this way with follow up data at two to 12 months in nine,² and Lababidi and Wu have reported equally promising results with the procedure in another 18 patients.³ This report describes a personal experience of 16 patients with pulmonary valve stenosis treated by percutaneous balloon valvuloplasty. Data from repeat catheterisation three to six months after the procedure are available in seven of the patients.

Percutaneous balloon angioplasty has been used for the treatment of other congenital cardiac malformations including aortic coarctation and hypoplasia of pulmonary arteries.^{4,5} I have used balloon angioplasty for the successful treatment of two post-

operative complications: stenosis of the lower limb of an atrial baffle in a patient with previous correction of complete transposition and residual supra-valvar pulmonary stenosis after debanding. Details of these two patients are also reported as these appear to be promising new applications of the technique.

Patients and methods

TECHNIQUE

The technique of balloon valvuloplasty has been described.¹⁻³ The technique involves several steps. Firstly, percutaneous cannulation of a femoral vein (preferably the right) is performed. An end hole catheter (for example, Goodale-Lubin) is then passed into a pulmonary artery (preferably the left) and a guidewire advanced through this catheter until its tip is well out into the lung field. The catheter is then withdrawn while the position of the guidewire in the pulmonary artery is maintained. The balloon catheter is then advanced over the guidewire until the pulmonary valve is midway between the radio-

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Accepted for publication 29 May 1985

opaque markers, which indicate the proximal and distal limits of the balloon. The balloon is then inflated with dilute contrast medium under pressure for approximately 20 seconds causing the pulmonary valve to rupture. The balloon is then deflated using negative pressure. This inflation is usually repeated once or twice during which time any air still in the balloon is aspirated into the inflating syringe.

The technique is simple and balloon valvuloplasty with preoperative and postoperative angiocardigrams and pressure measurements can be completed in 20–30 minutes. It may be useful, however, to describe the solutions to some of the problems that may be encountered. Firstly, an 18 mm balloon catheter (Medi-tech) (Medi-Tech Inc, Watertown, Mass 02171, USA) requires a No 10 French gauge (split) introducing sheath (Vygon, BP 7-95440, Ecoven, France); in practice I have found that it is often possible to advance these catheters directly through the skin incision without using an introducing sheath. Previous use of a No 9 French gauge vessel dilator will facilitate this. The initial skin incision must be of adequate size—5 mm or so. An assistant presses on the skin incision at the stage when the end hole catheter (together with any introducing sheath that was used) has been withdrawn and the balloon catheter is being threaded over the guidewire since there will be bleeding at this time. Secondly, it is important that the balloon be centred on the pulmonary valve. If the balloon is too proximal or too distal it may advance (or retract) itself during inflation without rupturing the valve. It is remarkable how much of this large balloon can be accommodated in the pulmonary arteries distal to the valve. As viewed with anteroposterior screening it may be difficult to appreciate that the balloon is wrongly positioned, and for this reason the practice in this hospital is to perform biplane angiography before balloon valvuloplasty. The position of the valve is marked on the lateral video monitor, and, provided that the patient's position is not changed, the balloon is correctly positioned using lateral screening as an aid (Fig. 1). It is important to use a balloon whose inflated diameter is slightly larger than the diameter of the valve ring. The diameter of the valve ring is measured from lateral angiocardigrams using the known diameter of the angiographic catheter to obtain the magnification factor. Where a previous angiographic study has been performed this measurement is used to select the appropriate balloon size. In patients between the ages of 1 and 7 years, however, I have found the valve ring to be between 12 and 16 mm in diameter; the 18 mm balloon has been effective in all patients and is therefore used routinely in those over the age of 1 year without previous measurement of the angiograms.

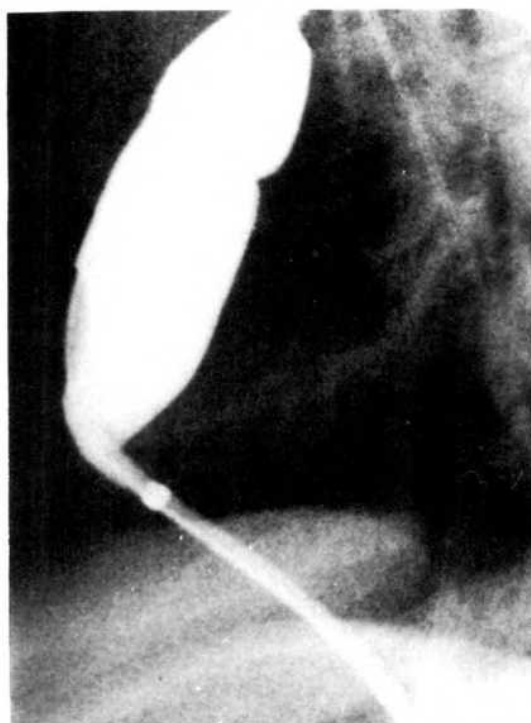


Fig. 1 Lateral angiogram showing the inflated angioplasty balloon positioned across the pulmonary valve. The valve is causing an indentation in the balloon, which disappears when the valve ruptures.

Results

PULMONARY VALVE STENOSIS

Balloon valvuloplasty was performed in 16 patients aged between 10 days and 17 years (Table). Preoperatively, right ventricular systolic pressure ranged between 37 and 87 mm Hg (mean (SD) 64(15) mm Hg) and pulmonary valve gradients between 19 and 71 mm Hg (mean 43(14) mm Hg). After valvuloplasty a satisfactory result (mean gradient after valvuloplasty 18 mm Hg) was obtained in all but three patients (cases 2, 4, and 5). With the exception of these three, gradients were reduced to ≤ 20 mm Hg (Fig. 2). Seven patients were recatheterised between three and six months after valvuloplasty; the good result was maintained in all but one (case 6), whose valve gradient had risen to 35 mm Hg (having originally been reduced from 60 to 18 mm Hg). Attempted repeat valvuloplasty in this 6 month old infant was frustrated by failure to advance an 18 mm balloon into the pulmonary artery. Repeat valvuloplasty was successfully performed in two other patients (cases 4 and 9) reducing

Table Angiographic data before (A) and after (B) balloon valvuloplasty, at follow up (C), and after repeat valvuloplasty (D) in patients with pulmonary valve stenosis

Case No	Age	Sex	RV systolic pressure (mm Hg)				RV to PA peak systolic gradient				Duration of follow up (months)
			A	B	C	D	A	B	C	D	
1	3 yr	F	87	33	28	—	68	13	5	—	6
2	3 yr	M	85	53	—	—	71	41	—	—	—
3	2½ yr	F	50	23	28	—	33	3	8	—	5
4	1½ yr	F	45	69	47	28	30	54	24	4	4
5	10 d	M	58	55	—	—	33	41	—	—	—
6	6 mnth	M	85	45	50	—	60	18	35	—	3
7	6 yr	M	60	45	30	—	42	18	20	—	3½
8	2 yr	M	64	32	40	—	50	18	20	—	3
9	7 yr	M	73	33	50	28	53	18	22	8	3
10	4 yr	M	60	40	—	—	35	11	—	—	—
11	2½ yr	M	37	31	—	—	19	7	—	—	—
12	9 mnth	M	50	28	—	—	33	4	—	—	—
13	2 yr	M	75	55	—	—	42	20	—	—	—
14	4 yr	M	65	33	—	—	47	8	—	—	—
15	5 yr	M	56	26	—	—	40	9	—	—	—
16	17 yr	F	70	30	—	—	37	7	—	—	—
Mean (SD)			63.8 (14.7)	39.4 (12.9)	39.0 (10.2)	28	43.3 (14.2)	18.1 (4.8)	19.1 (10.1)	6.0 (2.8)	

RV, right ventricular; PA, pulmonary arterial.

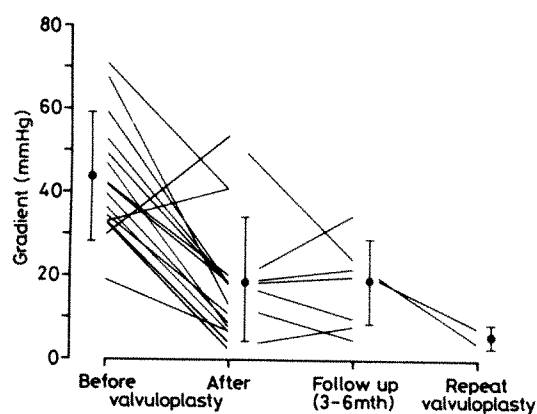


Fig. 2 Transverse gradients before and after balloon valvuloplasty and at follow up (3-6 months) in patients with pulmonary valve stenosis. The final gradients after repeat valvuloplasty at follow up in two patients are also shown. Bars denote mean (SD).

residual gradients of 24 and 22 mm Hg to 4 and 8 mm Hg respectively.

The first of the three patients with an unsatisfactory initial result was the youngest patient (case 5) in our series, who presented at 10 days of age with critical pulmonary valve stenosis and a dysplastic valve. After valvuloplasty the valve gradient rose from 33 to 41 mm Hg. Surgical valvotomy was then performed when it was found that, although the valve had been split, an intimal tear in the pulmonary artery had resulted in haematoma formation and therefore continuing (supravalve) pulmonary stenosis. The second patient (case 2) in whom

valvuloplasty was less than totally successful was aged 3 years and had had a previous surgical valvotomy for critical pulmonary stenosis as a neonate. The gradient was reduced from 71 to 41 mm Hg. Finally, in the third patient (case 4) the gradient actually rose from 30 to 54 mm Hg. In this patient the diameter of the valve ring was 15 mm; a 10 mm balloon was used at the initial valvuloplasty. Four months later the gradient was found to be 24 mm Hg and a second valvuloplasty was performed using an 18 mm balloon. The gradient was thereby reduced to 4 mm Hg.

RELIEF OF BAFFLE STENOSIS

Surgical correction of complete transposition (Mustard's operation) had been performed in one patient at the age of 11 months using a baffle of bovine pericardium. Signs of inferior caval obstruction lead to recatheterisation at the age of 2½ years. There was severe stenosis at the lower limb of the baffle and most of the lower body venous return was via the azygos system to the superior vena cava. Mean pressure in the inferior vena cava was 16 mm Hg and there was a mean gradient of 11 mm Hg between it and the systemic venous (left) atrium. Progressive dilatation of the stenosis was achieved using a 10 mm and then an 18 mm balloon. After the procedure the mean gradient had been reduced to 4 mm Hg and there was considerable angiographic improvement (Fig. 3).

RELIEF OF SUPRAVALVAR PULMONARY STENOSIS

One child had had a persistent ductus closed and had had pulmonary artery banding for ventricular septal defect in infancy. At 3 years of age the defect had

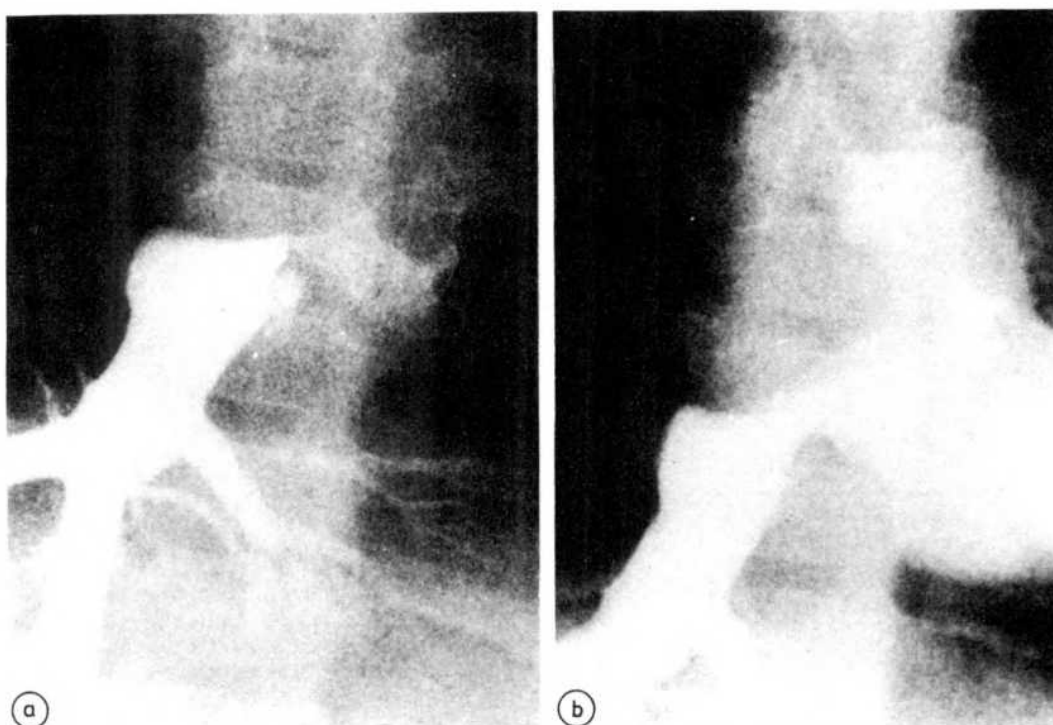


Fig. 3 Case 17: angiograms showing severe stenosis at the lower limb of an atrial baffle (Mustard's operation) before (a) and after (b) balloon angioplasty.

been closed and the pulmonary artery debanded. He presented to our hospital at the age of 6 years with signs and echocardiographic findings suggesting significant residual stenosis at the site of the band. Catheterisation showed a gradient of 23 mm Hg between proximal and distal main pulmonary artery. Balloon angioplasty (18 mm balloon) reduced the gradient to 3 mm Hg with improved angiographic appearances.

Discussion

That excellent relief of typical pulmonary valve stenosis can be achieved by balloon valvuloplasty is now well established.¹⁻³ It has yet to be established which, if any, patients are unsuitable candidates, and we do not yet know what will be the long term results obtained by this attractive technique. The patients reported here all had mild or moderate pulmonary stenosis; all had gradients of <100 mm Hg. Six of the patients, however, reported by Lababidi and Wu³ and two of those reported by Kan *et al*² had gradients >100 mm Hg and still had a significant reduction in the gradient—though some had residual

gradients of 35 to 82 mm Hg. Thus it would seem well worth attempting balloon valvuloplasty even in severe pulmonary stenosis, though a completely satisfactory result may not always be obtained. Of the three patients reported here who had an unsatisfactory result, one was due to the use of too small a balloon; the gradient was effectively abolished at a second study when a balloon of diameter slightly larger than that of the valve ring was used. Of the other two, one had had a previous surgical valvotomy and one was a neonate with a dysplastic valve. Kan *et al* report one patient with a dysplastic valve in whom the benefit of (repeated) valvuloplasty was not maintained,² and it may therefore be that patients with dysplastic valves or valves rendered dysplastic by previous surgery and scar tissue will be found to be less suitable for valvuloplasty than those with typical pulmonary stenosis and thin mobile "doming" valves. That balloon valvuloplasty can be successfully applied to neonates with critical pulmonary stenosis has been reported by Tynan *et al*,⁶ while at the other end of the age spectrum it has been successful in relieving pulmonary valve stenosis in a patient aged 59⁷ and was successful in a 17 year old

patient here. The procedure appears to be ideal treatment for patients with only moderate pulmonary stenosis in whom the disadvantages of surgery, cosmetic and otherwise, may outweigh the advantages. This would not be the case, however, if the procedure is shown to have an appreciable complication rate. In the present series the only complication occurred in the neonate with a dysplastic valve. The femoral vein was patent and easily cannulated in all of the patients who were recatheterised one to six months later. Neither Lababidi and Wu³ nor Kan *et al*² reported any complications other than the inevitable bradycardia and hypotension that occurs while the balloon is inflated. Nor did these authors detect the appearance of an early diastolic murmur in any of their patients either immediately or at follow up; this has been my own experience. What is observed is a decrease in the intensity of the systolic murmur.

Although the short term (2–12 months) follow up results reported here by Kan *et al*² show that the good result is maintained, the long term results remain speculative. Kan *et al* draw an analogy with the good long term results of the Brock procedure and speculate that similar results will be obtained by balloon valvuloplasty.² In this regard it is of interest to know whether valvuloplasty results in the splitting of valve tissue or merely (perhaps temporary) dilatation of the valve ring. I have experience of one patient in whom balloon valvuloplasty was performed during elective open heart surgery. Balloon inflation caused splitting of a commissure in this instance, and Lababidi and Wu reported an exactly similar experience in a single patient.³

Stretching of tissue is the likely mechanism for the success of balloon angioplasty in the present two postoperative cases. Here too it is not possible to know for how long the good result will be maintained, but even if palliation is only temporary the

procedure would appear to be worth while since surgical correction in each instance would have been complicated by the presence of scar tissue. The procedure can, presumably, be repeated if necessary. It is of interest that balloon dilatation also appears to be successful in stretching scar tissue in another postoperative complication—coarctation “restenosis”^{8,9}

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Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease

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SUMMARY In view of evidence suggesting an association of mild hypokalaemia with cardiac arrhythmia, the arrhythmogenic potentials of potassium losing and potassium sparing diuretic treatments were compared in a controlled prospective crossover study of 10 patients with mild hypertension and ischaemic heart disease. Mean (SEM) plasma potassium was 4.3(0.06) mmol/l and 3.3(0.07) mmol/l after potassium sparing and potassium losing treatments respectively. Blood pressure and volume depletion as assessed by weight change, plasma renin activity, and noradrenaline concentrations did not differ significantly in the two treatment periods. The potassium losing treatment phase was associated with an increased frequency of ventricular extrasystoles, a higher Lown grading during ambulatory electrocardiographic monitoring, prolonged duration and decreased phase 0 velocity of the monophasic action potential, a prolonged ventricular effective refractory period, and increased myocardial electrical instability as assessed by programmed ventricular stimulation.

It is concluded that minor changes in plasma potassium concentration are associated with increased ventricular electrical instability in patients with ischaemic heart disease. Mild hypokalaemia in such patients may predispose to life threatening arrhythmias and should be avoided.

Severe hypokalaemia (plasma potassium <3.0 mmol/l) is known to be associated with an increased incidence of cardiac arrhythmias.¹⁻⁴ This risk is further enhanced by the coexistence of myocardial ischaemia, cardiac failure, and digitalis treatment.⁵⁻⁷ There have been several reports implicating hypokalaemia of this magnitude as a primary cause of sudden cardiac arrest.⁸⁻¹⁰ The clinical importance of less severe hypokalaemia associated with diuretic treatment (plasma potassium 3.0-3.5 mmol/l), however, remains controversial. Some authorities maintain that any degree of hypokalaemia should be avoided,¹¹ whereas others state that only severe hypokalaemia warrants treatment.¹²⁻¹⁴ The controversy has been highlighted recently by the Multiple Risk Factor Intervention Trial¹⁵ and the re-analysis of the Oslo Study,¹⁶ both of which showed a greater incidence of sudden death in a

subgroup of diuretic treated hypertensive patients with minor electrocardiographic changes than in patients who were not taking diuretics. The implication of this finding was that diuretic treatment may have increased the risk of fatal cardiac arrhythmias, presumably through potassium or magnesium deficiency. Such a possibility must remain speculative until it can be shown in prospective controlled studies that cardiac electrical instability is consistently associated with mild hypokalaemia.

We investigated cardiac electrical instability in patients with mild hypertension and known coronary artery disease during treatment with a potassium losing diuretic and again after a similar period of treatment on a potassium sparing diuretic. We assessed myocardial electrical instability by several techniques and used an inpatient crossover design to provide controlled data. Because of a possible role of increased sympathetic activity during volume depletion, changes in plasma catecholamine concentrations, as well as renin/angiotensin/aldosterone activity, were also studied.

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Accepted for publication 14 May 1985

Patients and methods

The protocol was approved by the ethical committee of the Canterbury Hospital Board and all patients signed a consent form after a full explanation of the procedures. Eleven patients were recruited from the outpatient department. Their clinical details are given in Table 1. We used the following inclusion criteria: (a) the presence of mild hypertension (supine diastolic pressure phase 5, 90–100 mm Hg) measured on two consecutive outpatient visits; (b) a clinical history of typical effort angina; and (c) absence of clinically manifest atrial arrhythmias. Patients with impaired renal function, potassium abnormalities before the start of the study, known hypersensitivity to thiazides or amiloride, and those who were pregnant were excluded.

STUDY DESIGN

The study followed a randomised crossover design and consisted of eight weeks' treatment with a potassium sparing diuretic and eight weeks' treatment with a potassium losing compound. Nine patients received amiloride 10 mg twice daily as the potassium sparing diuretic. One patient received spironolactone (Aldactone A) 25 mg twice daily because of nausea attributed to amiloride. Eight patients received chlorthalidone 25 mg twice daily as the potassium losing drug. Two patients with chlorthalidone intolerance received cyclopenthiiazide 0.5 mg daily.

Five patients received the potassium sparing treatment first followed by the potassium losing treatment. In the remainder the order was reversed. When results were examined for an effect of treatment order none was found. Apart from sublingual nitrate for control of angina, no other drugs were used during the study. Nitrates were avoided for at least two hours before the blood pressure recording or any of the cardiac investigations described below.

Each eight week treatment phase ended with a 24 hour stay in hospital, during which a strict metabolic diet containing 180 mmol sodium and 60 mmol potas-

sium was taken. Hormone, biochemical, and cardiac studies were carried out during these two inpatient periods as described below.

CARDIAC INVESTIGATIONS

Blood pressure was recorded by means of an automated version of the London School of Hygiene sphygmomanometer¹⁷ with patients supine at 1000 after a five minute period of rest and again after they had stood for two minutes. The diastolic blood pressure was taken as phase 5 of the Korotkoff sounds. One observer made all the recordings.

Ambulatory electrocardiograms were recorded on an Oxford Instruments Medilog two channel recorder for 24 hours. The recorded tape was played back on to paper by means of the American Edwards Co Eliminator playback unit. A complete disclosure of the entire tape was read manually by two independent observers, both of whom were unaware of the identity of each tape. Tapes were analysed for frequency of ventricular extrasystoles per hour and for grading on the Lown scale.¹⁸ Paired observations on the frequency of extrasystoles accorded to within 1% and there was complete agreement on Lown grades.

Exercise testing—A multistage treadmill stress test was performed during each hospital admission (Bruce protocol). End points for testing were ST depression on the electrocardiogram, the development of symptoms, or a heart rate greater than 90% of the predicted maximum.

Electrophysiological testing—The monophasic action potential was obtained by a close suction electrode (ABO Co, Tully, Sweden) positioned in the apex of the right ventricle and recorded on photographic paper at 100 mm/s simultaneously with a surface electrocardiogram. Ten consecutive action potentials were manually digitised by means of a Wang desk top computer. The maximum height of each action potential was standardised to 100%, and the action potential duration was measured at each 10% interval of amplitude. The relative slope of the upstroke was taken as the 90–10% upstroke time. The frequency response of

Table 1 Patient characteristics

Case No	Age (yr)	Sex	Ejection fraction* (%)	Myocardial score†
1	63	M	49	7.4
2	48	M	64	8.0
3	55	M	40	5.4
4	60	F	82	10.6
5	56	M	79	10.2
6	60	F	73	0.0
7	63	M	70	9.6
8	51	F	56	7.6
9	57	M	62	2.0
10	52	M	60	6.4
11	58	M	71	6.4
Mean (SEM)	56(1.4)		64(3.8)	6.9(1.0)

*Measured during left ventricular angiography.

†Scored according to the method of Brandt *et al*²⁵

the system was DC 800 Hz. We estimated the effective refractory period of the right ventricle and attempted induction of ventricular tachycardia with programmed extrastimuli. A bipolar pacing electrode was positioned in the apex of the right ventricle and up to three extrastimuli were applied after a train of eight paced beats for tachycardia induction. The effective refractory period was determined with a precision of 2 ms. The protocol was based on a previously published method¹⁹ in which a maximum of three extrastimuli, but no rapid ventricular pacing, was used. The degree of myocardial electrical instability was assessed in two ways: firstly by a modification of a previously described system that takes into account both the number of repetitive responses as well as the number of stimuli required to produce the responses²⁰; and, secondly, by the induction of a non-sustained ventricular tachycardia of at least three beats at a rate exceeding 100 beats/minute. Tachycardia induction was regarded as positive when the arrhythmia could be initiated in this way on three separate occasions.

Hormonal and biochemical measurements were undertaken on venous blood drawn at 0800 after an overnight fast and 12 hours of recumbency, and were repeated after 60 minutes of upright posture. Plasma aldosterone,²¹ adrenaline and noradrenaline,²² and angiotensin II concentrations,²³ and plasma renin activity²⁴ were measured by standard techniques. Venous blood was also taken in the fasting state (0800) for measurement of plasma electrolyte concentrations. An arterial sample was drawn at the same time for blood gas and acid base determinations.

Coronary angiography was undertaken within three months of the study to assess the degree of coronary artery disease. A decrease of >50% in lumen diameter was taken to indicate significant stenosis. The coronary angiograms were scored by the method of Brandt *et al.*²⁵ This system allocates a numerical weighting to various portions of the left ventricle depending on the

extent of the vascular supply. The degree of narrowing of each vessel supplying the left ventricle is then graded and a score out of a maximum of 15 units calculated. This score provides a measure of the extent of myocardium affected by the coronary disease. Ejection fraction was calculated by digital callipers according to a previously described method.²⁶

Results

All but one patient completed the study without incident. The one exception was patient 11 (Table 1), who developed sustained ventricular tachycardia requiring DC shock during the electrophysiological study while in the potassium losing phase. He declined reinvestigation. Of the 11 patients, seven had abnormalities on the resting electrocardiogram recorded before the study. One showed voltage criteria for left ventricular hypertrophy, another had left anterior fascicular block, and in five there were non-specific T wave abnormalities.

Coronary angiography—Individual myocardial scores are given in Table 1. Five patients had single vessel disease, two had two vessel disease, and two had three vessel disease. One patient had only minor irregularities on the anterior descending coronary artery.

Blood pressure after diuretic treatment was not significantly different in the two groups. Mean lying pressure (mm Hg (SEM)) was 143(5.2) systolic and 86(2.3) diastolic after potassium sparing diuretics, and 135(3.4) systolic and 87(2.4) diastolic after potassium losing diuretics. Mean standing pressure was 135(4.9) systolic and 87(3.5) diastolic after potassium sparing diuretics, and 128(3.2) systolic and 81(3.8) diastolic after potassium losing diuretics.

Plasma electrolyte concentrations and biochemical indices (mean (SEM)) are given in Table 2. Plasma potassium concentration measured just before the study was 4.15(0.10) mmol/l. The plasma potassium

Table 2 Plasma biochemical indices (mean (SEM))

Index	Potassium losing phase	Potassium sparing phase	p value
Venous blood plasma (mmol/l).			
Potassium	3.3(0.07)	4.3(0.06)	<0.001
Sodium	137(0.41)	137(0.47)	NS
Chloride	98(1.49)	103(0.38)	<0.05
Carbon dioxide	27(0.5)	24(0.4)	<0.001
Glucose	5.8(0.2)	5.7(0.4)	NS
Urea	5.7(0.3)	5.6(0.4)	NS
Creatinine	0.08(0.01)	0.09(0.01)	NS
Urate	0.42(0.03)	0.37(0.03)	<0.05
Calcium	2.5(0.01)	2.4(0.03)	NS
Phosphate	0.9(0.07)	1.0(0.02)	NS
Arterial blood:			
pH	7.39(0.01)	7.37(0.02)	NS
Bicarbonate (mmol/l)	23.4(0.51)	20.5(0.81)	<0.02
Carbon dioxide (mm Hg)	38.5(1.0)	35.4(1.2)	<0.02

NS, not significant.

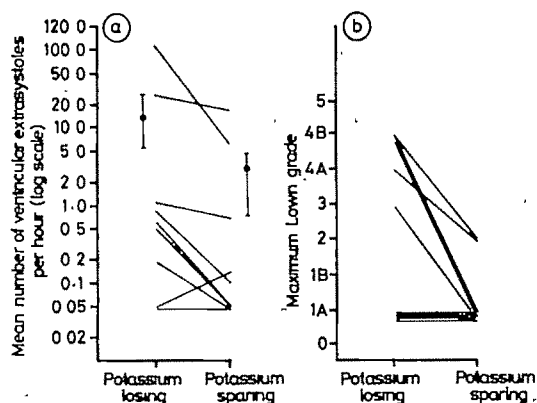


Fig. 1 (a) Mean number of ventricular extrasystoles per hour recorded over 24 hours in nine patients during ambulatory monitoring while taking potassium losing and potassium sparing diuretics. Results are shown for individual patients and as mean (SEM). (b) Maximum Lown grade ventricular extrasystoles recorded during 24 hour ambulatory monitoring.

concentration was significantly lower ($3.3(0.07)$ mmol/l) at the end of the potassium losing phase than at the end of the potassium sparing phase (plasma potassium $4.3(0.06)$ mmol/l ($p < 0.001$)). Total venous carbon dioxide and arterial bicarbonate values were significantly higher during the potassium losing phase. There was no significant difference between

treatment phases in plasma sodium, glucose, creatinine, urea, calcium, magnesium, and phosphate concentrations, but plasma chloride was lower ($p < 0.05$) and plasma urate was higher ($p < 0.05$) during the potassium losing phase than during the potassium sparing phase (Table 2).

Ambulatory electrocardiography—Because of a tape failure in one study, paired data were obtained in only nine patients. There was a significantly greater ($p < 0.05$) hourly frequency of ventricular extrasystoles and a higher Lown grade ($p < 0.05$) during the potassium losing phase than during the potassium sparing phase (Fig. 1). In seven of nine studies, the frequency of ventricular extrasystoles was greater during the potassium losing phase (Fig. 1). The Lown grade was higher in five patients during the potassium losing phase, but in the remaining four cases it was similar during both treatments (Fig. 1). There was no apparent relation between the frequency of ventricular extrasystoles or Lown grading and plasma potassium concentration.

Exercise testing—Exercise tests were positive in five patients, two on the basis of 1 mm horizontal ST segment depression, and angina developed in three. The mean duration of exercise was not significantly different in the two intervention phases (470 s vs 435 s for the potassium losing and sparing phases respectively). Only two patients had ventricular

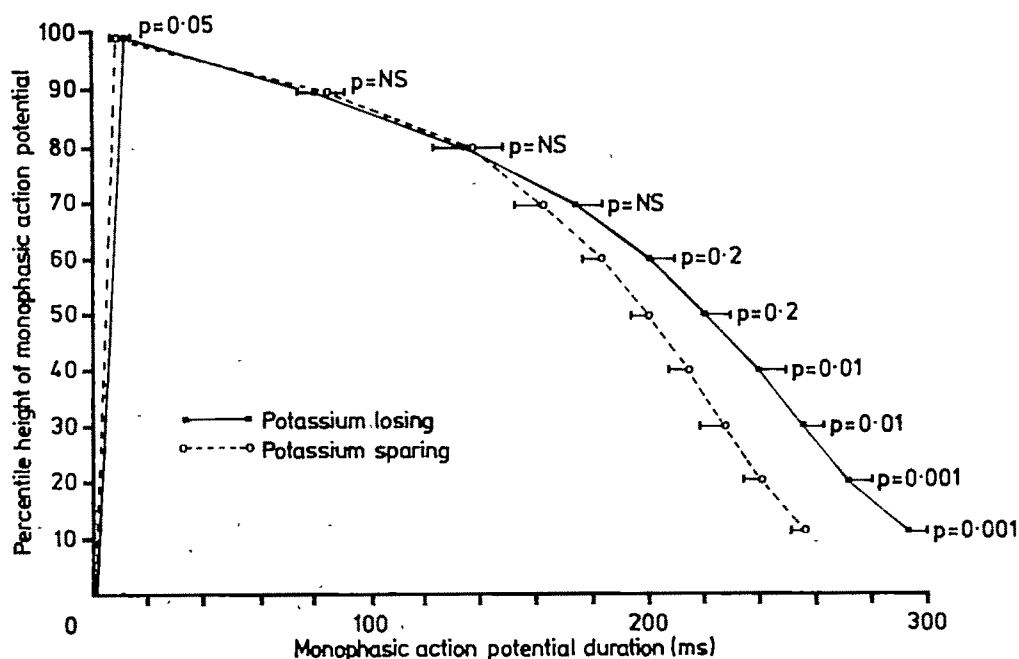


Fig. 2 Group mean time course of the monophasic action potential during potassium losing and potassium sparing treatment. *p* values were calculated by the paired *t* test.

extrasystoles during the exercise test. In both cases the ventricular extrasystoles occurred in the potassium losing phase and the same patients did not show any ventricular extrasystoles while taking the potassium sparing agents.

ELECTROPHYSIOLOGICAL STUDIES

Right ventricular monophasic action potential—The slope of the action potential upstroke was significantly ($p < 0.05$) steeper during the potassium sparing phase. Action potential duration at 50% repolarisation was prolonged during the potassium losing phase but this difference was not statistically significant. Action potential duration at 90% repolarisation, however, was significantly prolonged by hypokalaemia ($p < 0.001$) (Fig. 2).

Right ventricular effective refractory period—The effective refractory period of the right ventricle during the potassium losing phase was significantly prolonged (240(22) ms) compared with that during the potassium sparing phase (216(10.8) ms), ($p < 0.05$). The QT interval corrected for heart rate (0.45(0.03) s

vs 0.44(0.02) s) showed a 2% prolongation in the potassium losing phase, but this change did not reach statistical significance.

Tachycardia induction studies—One patient developed sustained ventricular tachycardia requiring DC shock during the potassium losing phase. Because he refused to continue in the study he did not complete the potassium sparing phase. Data from the 10 paired studies are shown in Fig. 3. Four patients developed tachycardia and had higher myocardial electrical instability scores during the potassium losing phase than during potassium sparing phase. In all but one of the remaining patients the scores were the same with both treatment regimens. In one patient the score during the potassium sparing phase was slightly higher than that during the potassium losing phase. Non-sustained ventricular tachycardia was induced in five patients during the potassium losing phase and in three patients during the potassium sparing treatment phase.

Heart rate—Heart rate (mean (SEM)) in the potassium losing phase was 80.0(11.9) beats/min and 79.9

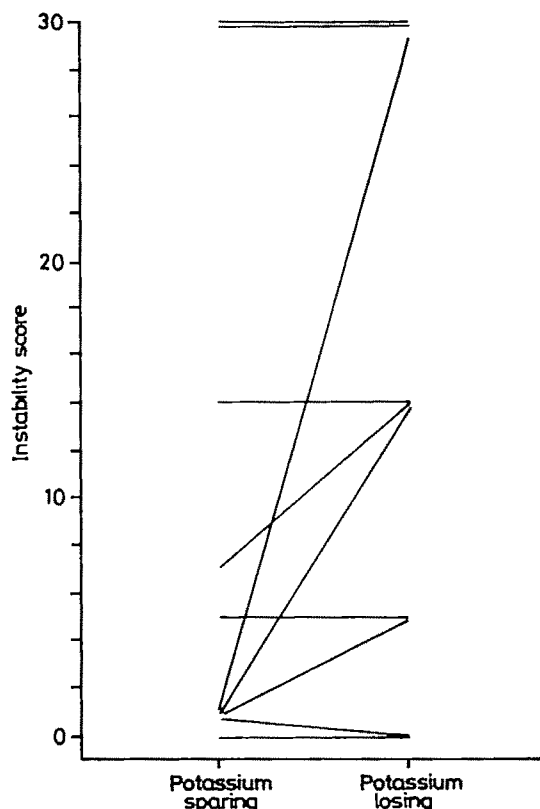


Fig. 3 Myocardial electrical instability score during potassium sparing and potassium losing treatment (see text for details of the scoring system).

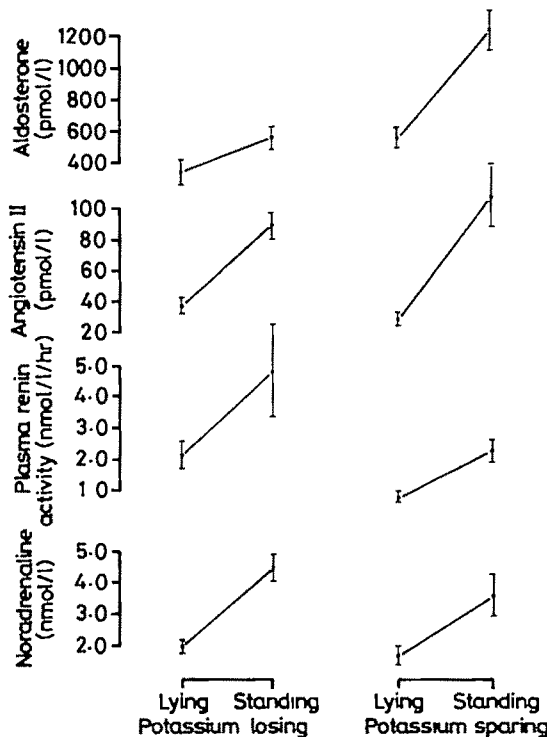


Fig. 4 Plasma concentrations of aldosterone, angiotensin II, renin activity, and noradrenaline measured when patients were lying down or standing up while on potassium sparing and potassium losing therapy. Values are mean (SEM). Plasma aldosterone (both lying and standing values) was significantly higher ($p < 0.001$) during potassium sparing treatment.

(11.0) beats/min during the potassium sparing phase.

HORMONE RESULTS

Hormone values when patients were lying or standing are shown in Fig. 4. Concentrations in supine patients and the rise in plasma noradrenaline and angiotensin II concentrations with erect posture were comparable in the two treatment phases. Plasma aldosterone, however, was significantly higher during treatment with potassium sparing diuretics ($p < 0.001$). Although plasma renin activity was lower in this phase, the difference was not statistically significant.

Discussion

Although severe potassium deficiency may precipitate life threatening cardiac arrhythmias, the effect of less severe hypokalaemia, particularly in patients with ischaemic heart disease, is controversial.¹¹⁻¹⁴ Recent studies have increased concern that conventional potassium losing diuretic treatment may be arrhythmogenic. The Medical Research Council mild hypertension study showed a significantly greater frequency of ventricular extrasystoles in patients treated with thiazide diuretics than in untreated control patients.²⁷ Others have shown similar changes during thiazide treatment that were partly abolished by potassium repletion.¹¹⁻¹² Observations of an increased incidence of ventricular fibrillation after acute myocardial infarction in hypokalaemic patients²⁸⁻²⁹ and of increased incidence of sudden death associated with high dose diuretic treatment of patients with mild hypertension⁵⁻¹⁵⁻¹⁶ add further to the concern. Although there were several explanations for these findings, the possibility of a causal relation between diuretic treatment and increased mortality in certain subgroups of hypertensive patients requires urgent clarification. There are, however, practical problems. To show a causal relation between hypokalaemia and sudden death in a small subgroup of patients requires a very large scale trial.¹⁴ In the absence of this information, the case for preventing diuretic induced hypokalaemia must be based on appropriately designed and controlled electrical trials showing a consistent association of increased myocardial electrical instability with potassium losing treatment.

We have examined prospectively in a randomised crossover controlled trial the effect of two short term diuretic treatments (one associated with potassium sparing and the other associated with potassium loss) in patients with mild essential hypertension and ischaemic heart disease. The hypotensive effect, and the degree of volume depletion as judged by body weight, activity of the renin angiotensin system, and catecholamine concentrations were comparable with the two treatments. There were significant differences

between the two treatments in plasma potassium, acid base, chloride and urate concentrations that accorded with the known actions of the diuretics. Plasma aldosterone was significantly higher in the potassium sparing phase as previously reported.³⁰ More importantly, consistent electrophysiological changes occurred in all patients during the potassium losing phase, and there was evidence of increased cardiac electrical instability as measured by several different standardised techniques. While animal and in vitro studies have shown that severe hypokalaemia (plasma potassium < 3.0 mmol/l) is associated with increased membrane potential negativity, increased rate of depolarisation, and increased duration of action potential³¹⁻³² the present study is the first to show that similar changes in action potential occur in man during modest changes in plasma potassium. Prolongation of action potential duration is indicative of delayed repolarisation. There was no significant difference between the two treatment phases at 50% repolarisation. This measurement includes phase 0, 1, and 2 of the action potential. Significant prolongation of the action potential was evident at 90% repolarisation during the potassium losing phase but not at 50%. This suggests that delayed repolarisation due to moderate hypokalaemia is mainly attributable to prolongation of phase 3 of the action potential. The action potential duration is heart rate dependent but rates during both treatment phases were identical; thus heart rate was not a factor responsible for the difference in delayed repolarisation in the potassium losing phase. Delayed repolarisation is usually estimated from the QT interval of the surface electrocardiogram. This is a measurement which is imprecise since it is often difficult to define the start and end of the QT segment in the surface electrocardiogram. There is no universal agreement on the choice of lead from which this measurement is to be made. In contrast to this the monophasic action potential can define the phases of excitation and repolarisation with a high degree of precision.³³ These factors probably explain why we found more consistent and significant changes in the potassium losing phase from analysis of the monophasic action potential than from the QT segment measurement. A generalised electrophysiological effect of the potassium losing treatment is supported by lengthening of the effective refractory period of the right ventricle in every patient.

If delayed repolarisation is homogeneous it may exert an antiarrhythmic effect. Heterogeneous repolarisation, however, has been shown to be associated with an increased risk of serious ventricular arrhythmias in congenital syndromes,³⁴ after myocardial infarction,³⁵ and after certain drugs.³⁶ To evaluate this effect further, we examined measures of cardiac electrical instability in patients at rest and during

exercise as well as during programmed intracardiac stimulation. From 24 hour recordings we found a significantly increased frequency of ventricular extrasystoles and a significantly higher Lown grading in the potassium losing phase—findings which are consistent with previous reports.¹¹⁻²⁷ Exercise induced ventricular extrasystoles occurred in only two of 20 studies and both patients were taking a potassium losing diuretic. This low frequency of ventricular extrasystoles during exercise (compared with that seen during ambulatory monitoring) is similar to previous reports.¹¹

Although these results are consistent with increases in cardiac electrical instability associated with the potassium losing treatment, it is doubtful whether such findings alone constitute proof of increased susceptibility to life threatening arrhythmias.³⁷⁻³⁸ We therefore sought additional information by inducing tachycardia by programmed intracardiac stimulation—a technique which is regarded as a reliable predictor of serious arrhythmias.³⁹⁻⁴¹ The electrical stability of the myocardium was assessed in two ways. Firstly, the frequency of induced ventricular tachycardia was measured, and secondly, we used a scoring system that takes into account both the number of repetitive responses as well as the number of stimuli required. Non-sustained ventricular tachycardia developed in five patients during the potassium losing phase and in three patients during the potassium sparing phase. In most patients the electrical instability score was similar for both diuretic treatments; thus overall there was no statistical difference between scores from the two phases of treatment. In those patients in whom there was a change (increase or decrease in score) electrical instability increased in four and decreased slightly in only one patient during the potassium losing phase of treatment.

While our observations of increased myocardial electrical instability may be explicable on the basis of potassium depletion, other factors could be involved. In keeping with previous reports¹¹ we found no correlation between plasma potassium concentration and indices of cardiac electrical instability. Despite the suggested importance of magnesium⁴² there were no significant differences in plasma magnesium between the two treatment phases. The possibility of diuretic induced hormonal changes, particularly in noradrenaline, contributing to increased electrical instability was investigated, with negative results. Further research is needed to evaluate the contribution of factors other than potassium.

As recently emphasised, no single technique is yet available to identify patients at high risk of sudden cardiac death.⁴³ Our study has examined myocardial electrical function in several ways and is not dependent

on a single technique for its conclusions. The results show that diuretic induced changes in plasma potassium are associated with demonstrable electrophysiological changes in all patients, that most showed increased frequency and complexity of ventricular extrasystoles, and that some had exercise induced arrhythmias. A smaller number were more susceptible to ventricular arrhythmias elicited by intracardiac stimulation. These findings, obtained in a small number of carefully studied patients, seem to reflect the clinical situation in which most patients may well have electrophysiological changes, but only a small proportion have major or fatal arrhythmias. It should be noted that our patients were not a high risk group; none had extensive coronary artery disease, history of significant arrhythmia, cardiac failure, or use of digitalis or other cardioexcitatory drugs. Since it is easier to prevent potassium deficiency than to treat it,⁴⁴ we conclude that a reduction in plasma potassium should be avoided in patients with ischaemic heart disease requiring diuretics.

We thank the Medical Research Council of New Zealand for financial support. Part of this study was undertaken when DES was in receipt of a grant from the Canterbury Medical Research Foundation.

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Usefulness of plasma renin activity in predicting haemodynamic and clinical responses and survival during long term converting enzyme inhibition in severe chronic heart failure

Experience in 100 consecutive patients

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SUMMARY The relation between plasma renin activity before treatment and the haemodynamic and clinical responses to converting enzyme inhibition was determined in 100 consecutive patients with severe chronic heart failure who were treated with captopril or enalapril. Initial doses of captopril produced significant increases in cardiac index and decreases in left ventricular filling pressure, mean arterial pressure, mean right atrial pressure, heart rate, and systemic vascular resistance that varied linearly with the pretreatment value for plasma renin activity. In contrast, there was no relation between the pretreatment activity and the magnitude of haemodynamic improvement after 1-3 months of treatment with the converting enzyme inhibitors, and, consequently, a similar proportion of patients with a high (>6 ng/ml/h; >4.62 mmol/l/h), intermediate ($2-6$ ng/ml/h; $1.54-4.62$ mmol/l/h), and low (<2 ng/ml/h; <1.54 mmol/l/h) pretreatment value improved clinically during long term treatment (64%, 60%, and 64% respectively). Long term survival after one, two, and three years was similar in the three groups. Estimating the degree of activation of the renin-angiotensin system by measuring pretreatment plasma renin activity fails to predict the long term haemodynamic or clinical responses to converting enzyme inhibitors in patients with severe chronic heart failure, and thus appears to be of limited value in selecting those patients likely to benefit from treatment with these drugs.

Although inhibition of the angiotensin converting enzyme with captopril and enalapril is of established value in the management of severe chronic heart failure,¹ there is no reliable means of selecting patients who are likely to improve during long term treatment with these drugs. Previous trials have indicated that 60-65% of patients with heart failure will benefit haemodynamically and clinically after 1-3 months' treatment with these agents,¹⁻⁴ but responders and non-responders do not appear to

differ with regards to pretreatment demographic, haemodynamic, or clinical variables.² Because of the ability of converting enzyme inhibitors to interfere with the renin-angiotensin system early investigators suggested that the responses to captopril and enalapril could be predicted by assessing plasma renin activity before treatment was started.⁵⁻⁸ Subsequent studies, however, found little relation between plasma renin activity and haemodynamic response and questioned the value of hormonal measurements as a means of selecting patients likely to benefit from treatment.⁹⁻¹¹ A major drawback of all of these previous studies is that they evaluated only the immediate effects of converting enzyme inhibition in small numbers of patients; unfortunately, short term haemodynamic assessments

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Accepted for publication 26 April 1985

of patients treated with captopril and enalapril are of limited value in predicting long term clinical outcome.¹²⁻¹⁴ No previous study has examined the usefulness of plasma renin activity in predicting the long term haemodynamic and clinical responses to these drugs in a large series of patients.

In this study we evaluated the relation between plasma renin activity and the haemodynamic and clinical effects of long term converting enzyme inhibition in 100 consecutive patients with severe chronic heart failure.

Patients and methods

The study population consisted of 100 (70 men, 30 women; aged 27-83 (mean 64) years) consecutive patients with severe chronic heart failure who received treatment with the converting enzyme inhibitors, captopril or enalapril, for at least two weeks and who had their plasma renin activity determined before the start of treatment. The cause of heart failure was ischaemic heart disease in 68 patients, primary myocardial disease in 25, and primary mitral or aortic valve regurgitation, or both, associated with severe left ventricular dysfunction in seven, four of whom had undergone valve replacement surgery. All patients had symptoms at rest or on minimal exertion but were evaluated while clinically stable.

HAEMODYNAMIC ASSESSMENT

Each patient received treatment with converting enzyme inhibitors under controlled conditions. For at least five days before entry into the study doses of digoxin and diuretics remained constant, all previous vasodilator drugs were withdrawn, and patients consumed a 2 g sodium diet. After completion of the initial observation period right heart catheterisation was performed with a triple lumen flow directed thermodilution catheter for the measurement of intracardiac pressures, and an arterial cannula was inserted into the radial artery to measure systemic pressures. Thermodilution cardiac outputs were determined in triplicate by a bedside cardiac output computer using iced injectate. Heart rates were derived from a continuously recorded electrocardiogram.

The following haemodynamic variables were determined repeatedly to ensure stability of the pre-treatment state before drug administration: mean arterial pressure, heart rate, pulmonary artery and pulmonary capillary wedge pressures, mean right atrial pressure, and cardiac output. Each of the 100 patients received an initial dose of 25 mg of captopril orally, after which all haemodynamic variables were determined every 30 minutes for three hours.

Patients were then treated with either captopril (75-450 mg daily, 86 patients) or enalapril (20-40 mg daily, 14 patients) for the next 1-3 months, during which time doses of digitalis, diuretics, and converting enzyme inhibitors remained unaltered and a 2 g sodium diet was maintained. At the end of the treatment period right heart catheterisation and arterial cannulation were again performed in 83 patients to assess the long term haemodynamic response to treatment; 17 patients did not undergo repeat evaluation because of death (three patients), refusal (three patients), a change in diuretic dosage (five patients), or physician preference (six patients). The protocol for the second haemodynamic evaluation was identical in all respects to that followed for the first study; haemodynamic variables were measured during uninterrupted treatment for three hours after the administration of captopril and for 4-6 hours after the administration of enalapril.

HORMONAL AND CLINICAL DETERMINATIONS

Blood samples for determining plasma renin activity by radioimmunoassay were collected just before the initial dose of captopril. All samples were drawn at a similar time of day, while the patient was receiving a constant 2 g sodium diet, after 4-12 hours lying supine, and 12-24 hours after taking the last dose of diuretic. Under these conditions, the reproducibility of our determinations of plasma renin activity in 52 patients with congestive heart failure on consecutive days was excellent: $r=0.89$ for $\log_e(\text{day}_2\text{PRA}) = 0.88 \times \log_e(\text{day}_1\text{PRA}) + 0.15$, where PRA is plasma renin activity.

Changes in the clinical state of each patient after 1-3 months' treatment with captopril or enalapril were assessed in relation to the presence or absence of dyspnoea and fatigue at rest and during daily activities. Patients who improved clinically after 1-3 months continued to receive these drugs in addition to digitalis and diuretics. Patients who did not improve continued to receive treatment with the converting enzyme inhibitors according to the preference of their referring doctor. Patients who experienced adverse reactions were treated with lower doses of these drugs (after the side effect had subsided); treatment was stopped if the adverse reaction recurred with rechallenge. All patients were reassessed clinically at intervals of 1-2 months. Long term survival was assessed from the first day of treatment to July 1984; follow up data were available in 97 of 100 patients.

DATA ANALYSIS

Mean systemic arterial pressures were determined by electronic filtration. Left ventricular filling pres-

Table 1 Correlation coefficients for the relation between plasma renin activity and changes in various haemodynamic variables after first doses of captopril and after long term converting enzyme inhibition

Variables	First dose	Long term
Cardiac index	0.49*	0.09
Left ventricular filling pressure	0.47*	0.19
Mean arterial pressure	0.45*	0.27**
Mean right atrial pressure	0.34*	0.18
Heart rate	0.28**	0.10
Systemic vascular resistance	0.46*	0.19

* $p < 0.001$; ** $p < 0.05$, levels of significance for correlation coefficients (r)

sure was measured as the mean pulmonary capillary wedge pressure or as the pulmonary artery diastolic pressure after it had been shown to be identical with wedge pressure. Derived haemodynamic variables were calculated as follows: cardiac index = CO/body surface area (l/min per m^2) and systemic vascular resistance = $80 \times (MAP - MRAP) / CO$ (dyn $s\ cm^{-5}$) where CO is cardiac output, MAP mean arterial pressure, and MRAP mean right atrial pressure.

During both short term and long term treatment, the haemodynamic responses to converting enzyme inhibition were assessed at peak drug effect on left ventricular filling pressure and systemic vascular resistance (1.0(0.5) h after captopril and 3.0(1.0) h after enalapril).

Patients were divided into three groups based on their pretreatment plasma renin activity: low (< 2 ng/ml/h; < 1.54 mmol/l/h), intermediate (2–6 ng/ml/h; 1.54–4.62 mmol/l/h), and high (> 6 ng/ml/h; > 4.62 mmol/l/h). These ranges were based on normal values in our laboratory (2–6 ng/ml/h (1.54–4.62 mmol/l/h) while the patient was lying supine and taking a salt restricted diet), and is similar to the classification scheme used by others.^{15,16} Qualitative and quantitative differences between the three groups were compared by the χ^2 test and by one way analysis of variance respectively. The hypotheses that plasma renin activity and the haemodynamic responses to treatment were significantly related were tested by least squares linear regression analysis. Survival curves were calculated by life table analytical methods. Group data are expressed as mean (standard error of the mean).

Results

HAEMODYNAMIC RESPONSES TO CONVERTING ENZYME INHIBITION

First doses of captopril produced significant ($p < 0.001$) increases in cardiac index and decreases in left ventricular filling pressure, mean arterial pres-

sure, mean right atrial pressure, heart rate, and systemic vascular resistance that varied linearly ($p < 0.05$ to 0.001) with the pretreatment plasma renin activity (Table 1 and Fig. 1). In contrast, there was no correlation between pretreatment plasma renin activity and the magnitude of the haemodynamic response to long term converting enzyme inhibition (Fig. 1, Table 1). Only the weak correlation between plasma renin activity and the long term decrease in mean arterial pressure ($r = 0.27$) was significant ($p < 0.05$), and this was because of the large number of patients studied.

CLINICAL RESPONSES TO CONVERTING ENZYME INHIBITION

After 1–3 months' treatment, 23 of 36 (64%) patients with low plasma renin activity, 25 of 42 (60%) patients with intermediate activity, and 14 of 22 (64%) patients with high activity improved clinically by at least one New York Heart Association functional class. Pretreatment haemodynamic and clinical variables in these three groups were similar, except for a slightly lower heart rate in patients with low activity ($p < 0.05$ vs groups with intermediate and high activity) (Table 2). After 6, 12, 18, 24, 30, and 36 months long term survival in the low, intermediate, and high activity groups was similar (Fig. 2). All but 18 of 100 patients had received treatment with captopril or enalapril until their most recent follow up visit or until within four weeks of their death.

Discussion

The findings of the present study indicate that the pretreatment measurement of plasma renin activity cannot be used to select patients with severe chronic heart failure who will benefit from long term treatment with converting enzyme inhibitors. Although plasma renin activity varied linearly to a modest but significant degree with the immediate response to captopril, it did not correlate with the haemodynamic effects of long term treatment. Categorisation of patients into high, intermediate, and low activity groups did not predict long term clinical benefits or survival. There appears, therefore, to be little reason for measuring plasma renin activity before treatment is started with converting enzyme inhibitors in patients with congestive heart failure.

In so far as plasma renin activity is an accurate marker of angiotensin dependent vasoconstriction, we were not surprised to find a significant relation between plasma renin activity and the haemodynamic responses to first doses of captopril. Similar findings have been reported by others^{5–8}; the failure of some investigators to confirm these

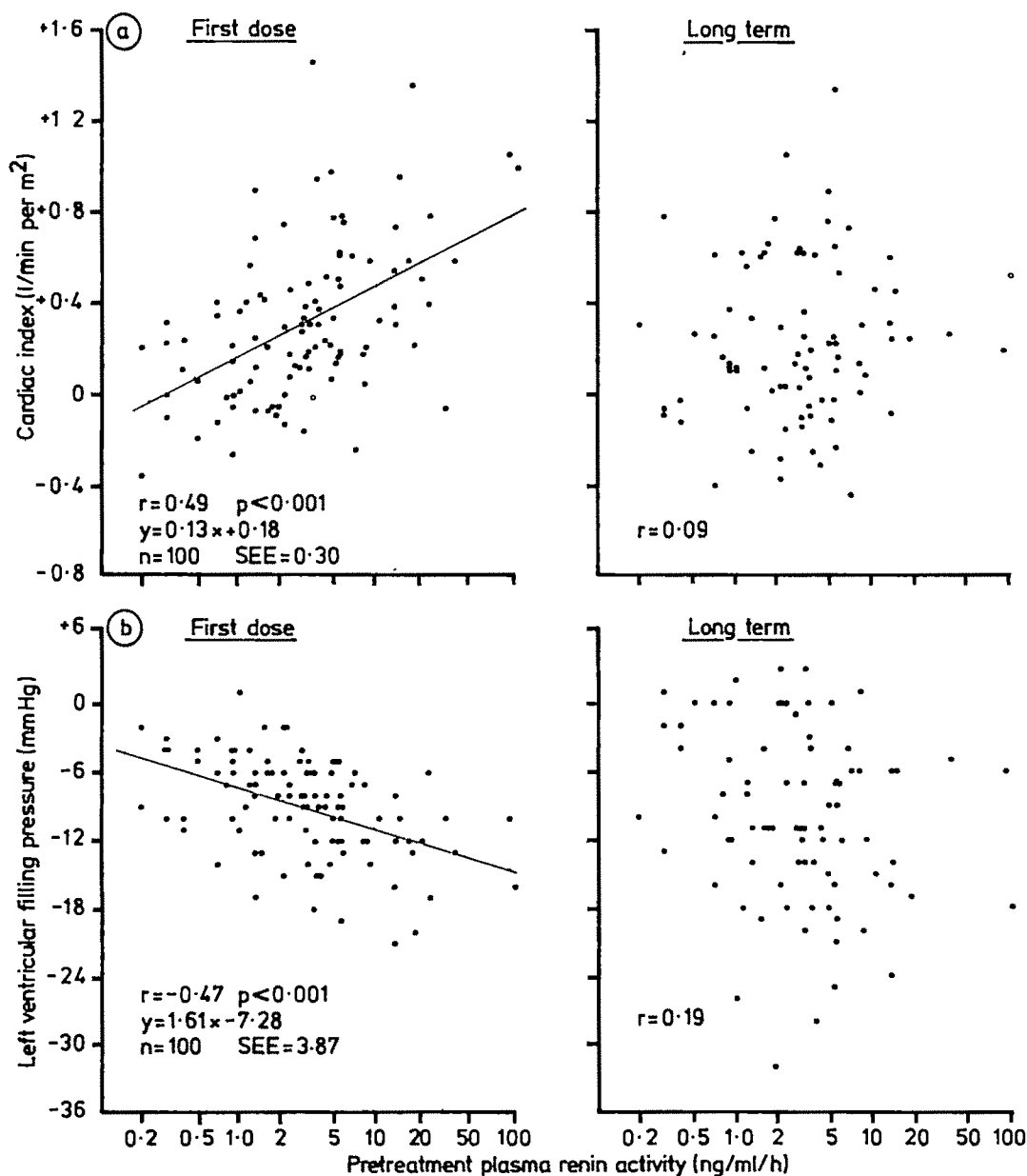


Fig 1 Relation between pretreatment plasma renin activity and changes in (a) cardiac index and (b) left ventricular filling pressure after first doses of captopril and long term converting enzyme inhibition in patients with severe chronic heart failure. A significant relation was noted for both variables after first doses but not during long term treatment. Conversion: traditional to SI units—plasma renin activity: $1 \text{ ng/ml/h} \approx 0.77 \text{ mmol/l/h}$.

Table 2 Pretreatment haemodynamic and clinical variables in patients with heart failure grouped according to values for plasma renin activity before converting enzyme inhibition. Values are mean (SEM) unless stated otherwise

Variables	Low (< 2 ng/ml/h)	Intermediate (2-6 ng/ml/h)	High (> 6 ng/ml/h)	p value*
Age (yr)	66.9 (1.8)	61.7 (2.0)	65.6 (1.7)	NS
No. of patients (M/F)	25/11	30/12	15/7	NS
No. of patients with:				
Ischaemic heart disease	21	29	18	NS
Primary cardiomyopathy	12	9	4	NS
Primary valve disease	3	4	0	NS
Cardiac index (l/min per m ²)	1.78 (0.08)	1.81 (0.07)	1.64 (0.06)	NS
Left ventricular filling pressure (mm Hg)	25.7 (0.7)	26.5 (0.7)	27.7 (0.9)	NS
Mean arterial pressure (mm Hg)	87.1 (2.7)	82.2 (2.0)	78.8 (2.9)	NS
Mean right atrial pressure (mm Hg)	11.4 (1.0)	11.6 (0.9)	12.3 (1.5)	NS
Heart rate (beats/min)	80.7 (2.0)	86.7 (2.0)	88.8 (3.3)	< 0.05
Systemic vascular resistance (dyn s cm ⁻⁵)	2110 (133)	1908 (80)	2019 (147)	NS

*Significance of difference between the three groups.

Conversion, traditional to SI units — plasma renin activity: 1 ng/ml/h $\approx$ 0.77 mmol/l/h.

observations was probably related to their evaluation of small numbers of patients with a narrow range of values for plasma renin activity.⁹⁻¹¹ The relation that we found between plasma renin activity and short term response, however, was not as striking as has been reported previously,⁵⁻⁸ partly because many of our patients with low plasma renin activity showed pronounced early haemodynamic effects. This unexpected response may be related to the ability of converting enzyme inhibitors to interact with other hormonal systems,¹⁷⁻¹⁹ or to the ability of renin and angiotensin to act as local tissue hormones, so that circulating concentrations of these substances may not reflect their concentration at active sites in the peripheral vasculature.^{20,21}

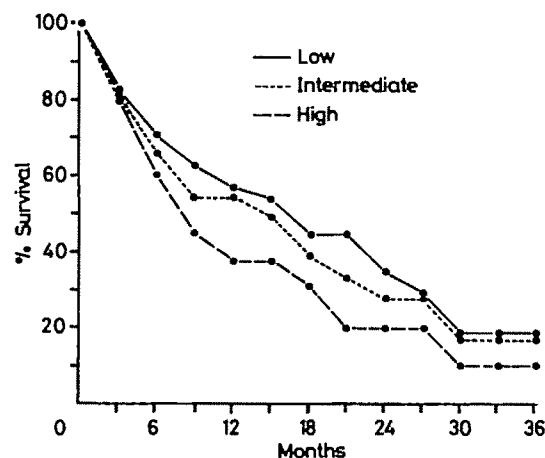


Fig. 2 Long term survival in patients with severe chronic heart failure treated with converting enzyme inhibitors grouped into low ($n=36$), intermediate ($n=42$), and high renin ($n=22$) cohorts. The small differences in survival between the groups were not significant.

The modest relation that we found between pretreatment plasma renin activity and the initial haemodynamic effects of captopril was no longer seen after 1-3 months of converting enzyme inhibition; a similar time dependent dissociation between haemodynamic and hormonal variables has been noted in hypertensive subjects.^{22,23} These observations can be explained by our previous finding that the magnitude of the response to converting enzyme inhibition can change dramatically during the course of treatment. Some patients with heart failure who respond initially to captopril fail to show sustained effects with prolonged treatment; conversely, many patients who do not respond initially benefit only during long term treatment.¹² This delayed response to converting enzyme inhibition is common in patients with heart failure¹² and may result from the reversal of a slow pressor response to angiotensin,^{23,24} from a diuretic effect of captopril and enalapril that follows their suppression of aldosterone,^{6,12} or from the ability of these drugs to produce a long term reduction in the circulating concentrations of other vasoconstrictor hormones (catecholamines and vasopressin).^{18,19} All these factors (acting alone or in concert) probably explain why the haemodynamic response to first doses of captopril bears little relation to its haemodynamic effects during long term treatment and thus fails accurately to predict the clinical response to long term converting enzyme inhibition.¹²⁻¹⁴

Our finding that plasma renin activity did not predict long term survival in our patients with severe heart failure is of interest. Massie and coworkers have shown that one of the principal prognostic factors in patients with heart failure is their response to treatment with vasodilators²⁵; patients who show favourable clinical effects fare better than those who do not benefit from treatment. In so far as plasma renin activity did not determine clinical response we

were not surprised that it also failed to predict long term survival. These findings, however, should not be construed to suggest that the renin-angiotensin system does not play a role in determining long term prognosis. All our patients were treated with converting enzyme inhibitors, which would be expected to neutralise any direct detrimental influence that angiotensin II might exert on mortality; if this neutralisation was complete, patients with a high plasma renin activity would fare as well as those with low or intermediate values. Accordingly, in order to determine if the renin-angiotensin system does exert a detrimental effect on survival, the relation between the degree of activation of the system and prognosis must be assessed in patients who are not treated with converting enzyme inhibitors. Such a deleterious role for angiotensin II has been postulated in patients with systemic hypertension and hepatic cirrhosis and, more recently, in patients with congestive heart failure, most of whom did not receive treatment with captopril or enalapril.²⁶⁻²⁸

Our findings must be interpreted cautiously. Previous claims of the value of plasma renin activity in predicting clinical events were based on studies performed in hypertensive patients who were in sodium balance while taking no drugs.²⁷ Our patients had severe heart failure, were receiving diuretic drugs, and may not have achieved sodium balance despite great efforts to keep sodium intake and body weight constant before entry into the trial. Furthermore, patients with heart failure may alter their dependence on angiotensin II during the course of their disease if dietary intake of sodium or the dose of diuretics are changed (although such changes were not permitted in the present study) or their clinical state deteriorates.^{29,30} Accordingly, it is unrealistic to expect that a single measurement of plasma renin activity, although determined under steady state conditions, would be able to estimate reliably the present or future role of the renin-angiotensin system in the pathogenesis of heart failure in an individual patient; hence, it cannot be used to predict the response to interventions that interfere with angiotensin II formation.

MP is the recipient of a Research Career Development Award from the National Heart, Lung and Blood Institute, Bethesda, Maryland, USA.

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USES: Frumil is a potassium sparing diuretic indicated for oedema, particularly in conditions where potassium conservation is important, e.g. congestive cardiac failure, nephrosis, corticosteroid therapy and oestrogen therapy, and ascites associated with cirrhosis. **DOSAGE:** Adults: One tablet each morning, increasing to two if necessary. **CONTRA-INDICATIONS:** Hyperkalaemia, concomitant potassium supplements, electrolyte imbalance, severe progressive renal disease, anuria, acute renal failure, precoma states associated with cirrhosis, known sensitivity to frusemide or amiloride. Safety in children, or during pregnancy and lactation has not been established. **PRECAUTIONS, WARNINGS:** Diabetes, gout, renal or hepatic insufficiency, impairment of micturition, concomitant cardiac glycosides or cephaloridine therapy. Plasma potassium monitoring is recommended. The activity of antihypertensive agents may be potentiated. Hyponatraemia, hypochloroemia and raised blood urea nitrogen may occur during vigorous diuresis. **SIDE-EFFECTS:** Malaise, gastric upset, nausea, vomiting, diarrhoea and constipation may occur. Skin reactions necessitate withdrawal. Rare complications may include bone marrow depression, minor psychiatric disturbances, disturbances in liver function tests and reversible deafness. **PHARMACEUTICAL PRECAUTIONS:** Store in a cool dry place. Protect from light. **PRODUCT LICENCE NUMBER:** 0152/0183
LEGAL CATEGORY: POM **PACKAGE QUANTITIES:** Cartons of 28 tablets consisting of 2 calendar foils of 14 tablets. **BNHS COST PER DAY:** 13.5p-27p.

FRUMIL A logical improvement

BERK
Pharmaceuticals Ltd.
Eastbourne, England
Glasnevin, Dublin 11.

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Longer-lasting relief for the angina patient

MONO-CEDOCARD 20
(isosorbide mononitrate)

and **MONO-CEDOCARD 40**
(isosorbide mononitrate)

for patients who require increased dose therapy

PRESCRIBING INFORMATION

Presentation: Round white tablets, embossed "Mono CC" (Mono-Cedocard 20) or "40 Mono 40" (Mono-Cedocard 40) on one side, reverse side scored, containing 20mg or 40mg isosorbide 5-mononitrate.

Uses: For the prophylaxis of angina pectoris. Isosorbide mononitrate, the active constituent of Mono-Cedocard, is the major active metabolite of isosorbide dinitrate. It has significant vasodilator activity, the strongest effect being exerted on the venous system, and a lesser effect on the arterial circulation. As a consequence, the heart has less work to perform against diminished resistance, and therefore oxygen requirement is reduced. After oral administration, isosorbide mononitrate is well absorbed, a haemodynamic effect being measurable within 15-20 minutes. In contrast to isosorbide dinitrate, the mononitrate is not subject to first-pass metabolism.

Dosage and Administration: For oral administration.

Adult dose: Mono-Cedocard 20 — one or two tablets to be taken two or three times daily. Mono-Cedocard 40 — one tablet twice a day taken after meals. The tablets should be swallowed (without chewing) with a little water.

Dosage for the Elderly: The dosage of nitrates in cardiovascular disease is usually determined by patient response and stabilisation. Clinical experience has not necessitated alternative advice for use in elderly patients.

There is no dose recommendation for children.

Contra-indications, Warnings, etc.

Contra-indications: In acute myocardial infarction with low filling pressures. In acute circulatory failure (shock, vascular collapse). When blood pressure is very low. During the first three months of pregnancy.

Cautionary Restrictions: Consumption of alcohol should be avoided during treatment as reaction

Adverse effects: Generally, no serious effects are to be expected. Headache, dizziness, fatigue, palpitations, orthostatic hypotension and flushing may occur, especially at the beginning of treatment. These reactions can usually be controlled by a temporary dosage reduction.

Treatment of overdosage: Gastric lavage, passive exercise of the extremities of the recumbent patient will promote venous return.

Pharmaceutical Precautions:

Storage: Protect from heat and moisture.

Legal Category:

Mono-Cedocard 20: POM

Mono-Cedocard 40: P

Package Quantities:

Mono-Cedocard 20: 100 tablets

Mono-Cedocard 40: 60 tablets

Further Information:

The plasma half-life of isosorbide mononitrate is 4.2 hours.

Product Licence Number

Mono-Cedocard 20: PL 0424/0040

Mono-Cedocard 40: PL 0424/0054

Basic NHS Cost

Mono-Cedocard 20: £8.77 per 100 tablets

Further information available from:



Effects of enalapril in heart failure: a double blind study of effects on exercise performance, renal function, hormones, and metabolic state

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SUMMARY Several studies have shown symptomatic and haemodynamic improvement after the introduction of angiotensin converting enzyme inhibitors in patients with heart failure treated with diuretics. The concomitant long term effects of the new orally effective long acting angiotensin converting enzyme inhibitor, enalapril, on symptoms, exercise performance, cardiac function, arrhythmias, hormones, electrolytes, body composition, and renal function have been further assessed in a placebo controlled double blind cross over trial with treatment periods of eight weeks. Twenty patients with New York Heart Association functional class II to IV heart failure who were clinically stable on digoxin and diuretic therapy were studied. Apart from the introduction of enalapril, regular treatment was not changed over the study period; no order or period effects were noted. Enalapril treatment significantly improved functional class, symptom score for breathlessness, and exercise tolerance. Systolic blood pressure was significantly lower on enalapril treatment. Echocardiographic assessment indicated a reduction in left ventricular dimensions and an improvement in systolic time intervals. In response to enalapril, the plasma concentration of angiotensin II was reduced and that of active renin rose; plasma concentrations of aldosterone, vasopressin, and noradrenaline fell. There were significant increases in serum potassium and serum magnesium on enalapril. Glomerular filtration rate measured both by isotopic techniques and by creatinine clearance declined on enalapril while serum urea and creatinine rose and effective renal plasma flow increased. Body weight and total body sodium were unchanged indicating that there was no overall diuresis. There was a statistically insignificant rise in total body potassium, though the increase was related directly to pretreatment plasma renin ($r=0.5$). On enalapril the improvement in symptoms, exercise performance, fall in plasma noradrenaline, and rise in serum potassium coincided with a decline in the frequency of ventricular extrasystoles recorded during ambulatory monitoring. Adverse effects were few.

In patients with heart failure, enalapril had a beneficial effect on symptoms and functional capacity. The decline in glomerular filtration rate on enalapril may not be beneficial in early heart failure.

The three principal groups of drugs used to treat heart failure are diuretics, digitalis preparations, and

vasodilators. Whereas the place of diuretics is firmly established, the value of digitalis in the long term treatment of heart failure with sinus rhythm remains controversial^{1,2} and the results of controlled trials of vasodilators are conflicting.³⁻⁶

Angiotensin converting enzyme inhibitors should have all the advantages of conventional vasodilators

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Accepted for publication 28 May 1985

in the treatment of cardiac failure together with several substantial additional benefits. Angiotensin II is an important stimulus to aldosterone secretion⁷; and lowering plasma angiotensin II by angiotensin converting enzyme inhibition should reduce aldosterone secretion and thus facilitate diuresis while also correcting any deficiency of potassium and magnesium associated with diuretic therapy and aldosterone excess.⁸⁹

Hyperaldosteronism is particularly likely to occur with prolonged diuretic treatment of heart failure and the resulting electrolyte abnormalities predispose patients to cardiac arrhythmias.¹⁰¹¹

The high circulating concentrations of angiotensin II encountered in heart failure can stimulate excessive secretion of vasopressin¹² which hinders diuresis.¹³ Reduction of vasopressin secretion by angiotensin converting enzyme inhibition should promote fluid excretion. Angiotensin II also stimulates the sympathetic nervous system at various sites¹⁴ and inhibits vagal transmission¹⁵; angiotensin converting enzyme inhibition will reverse these actions.¹⁶¹⁷ Angiotensin II also has direct renal actions in cardiac failure. Despite a profound reduction in renal blood flow,¹⁸ glomerular filtration rate and urea excretion¹⁸¹⁹ are well preserved until a late stage of heart failure. This maintenance of renal function is mainly the result of the intrarenal actions of angiotensin II which increases efferent glomerular arterial tone²⁰ and enhances the efficiency of vasa recta countercurrent exchange mechanisms.¹⁹ In

late cardiac failure, however, excessive intrarenal angiotensin II can cause glomerular shutdown with rapidly advancing uraemia and hyponatraemia.¹⁹ Thus angiotensin converting enzyme inhibition might benefit the kidney in advanced heart failure, but at earlier stages might worsen some aspects of renal function.

Several well controlled trials of angiotensin converting enzyme inhibition in cardiac failure have now shown clinical benefit,²¹⁻²⁵ although, to our knowledge, only one using captopril has concurrently evaluated symptoms together with metabolic, hormonal, and renal changes.²⁶

We report here the effects of enalapril, a new long acting angiotensin converting enzyme inhibitor, determined in 20 patients with heart failure in a trial with a double blind cross over design for within patient comparisons. In addition to assessing symptoms and exercise performance we measured renal function, serum and total body electrolytes, the renin-angiotensin system, and plasma aldosterone, vasopressin, and catecholamine concentration.

Patients and methods

PATIENT SELECTION

We studied 20 patients with chronic heart failure caused by ischaemic heart disease (nine), congestive (dilated) cardiomyopathy (eight), or severe left ventricular dysfunction after successful valve replacement (three) who were in New York Heart Associ-

Table 1 Biochemical variables measured at baseline, during enalapril treatment, and during placebo treatment

		Baseline	Enalapril	Placebo	Significance*
Serum sodium (mmol/l) (n = 19)		139 (4)	138 (4)	139 (3)	NS
Serum potassium (mmol/l) (n = 19)		3.8 (0.3)	4.2 (0.3)	3.7 (0.3)	p < 0.00001
Serum magnesium (mmol/l) (n = 19)		0.755 (0.183)	0.835 (0.081)	0.817 (0.080)	p < 0.05
Serum urea (mmol/l) (n = 19)		6.4 (2.0)	8.0 (2.4)	6.4 (1.9)	p < 0.001
Serum creatinine (μ mol/l) (n = 19)		100 (24)	110 (31)	101 (24)	p < 0.01
Total body sodium (mmol) (n = 16)		3385 (621)	3267 (512)	3390 (575)	NS
Total body potassium (mmol) (n = 16)		2659 (619)	2787 (635)	2741 (669)	NS
Plasma active renin (μ U/ml) (n = 19)					
	Mean	81	695	98	
	Median	47	406	61	
	Range	3-532	3-2256	3-673	p < 0.00001
Plasma angiotensin II (pmol/l): (n = 18)					
	Mean	39	14	34	
	Median	31	13	29	
	Range	1-160	4-35	1-83	p < 0.005
Plasma aldosterone (ng/dl). (n = 19)					
	Mean	14	10	16	
	Median	10	8	9	
	Range	6-37	4-39	3-85	p < 0.05
Plasma noradrenaline (nmol/l) (n = 16)		3.2 (1.4)	2.2 (0.8)	3.2 (1.2)	p < 0.002
Plasma adrenaline (nmol/l) (n = 16)		0.3 (0.1)	0.3 (0.2)	0.4 (0.2)	NS
Plasma vasopressin (pg/ml). (n = 18)					
	Mean	1.9	1.3	2.2	
	Median	1.6	1.1	1.5	
	Range	0.3-5.1	0.2-3.6	0.5-7.8	p < 0.02

*Statistical significance of difference between enalapril and placebo. Values are mean (SD) unless otherwise stated.

Conversion: traditional units to SI—Aldosterone: 36.1 ng/dl = 1000 pmol/l. Vasopressin: 1 pg/ml = 0.923 pmol/l

ation class II or IV. Mean (SD) duration of symptoms at entry was 18 (13) months. All had had symptoms for more than three months. Patients with serious concomitant disease or appreciable valvar regurgitation were excluded. All vasodilators were withdrawn at least one month before investigation and doses of frusemide (mean (SD) daily dose 124 (57) mg/day) and digoxin (mean daily dose 0.22 (0.06) mg/day) were held constant. One patient refused frusemide and continued on bumetanide 3 mg/day. Four patients were also on amiloride 10–15 mg/day, five on potassium chloride (1.8–2.4 g/day), one on hydrochlorothiazide 100 mg/day, and one had been treated with amiodarone 400 mg/day for the previous two years; doses of these agents were also held constant through the trial.

STUDY DESIGN

Patients were assessed and were familiarised with study procedures including repeated exercise tests four weeks before the start of the study. They were then admitted for 10 days for full initial assessment before being randomly allocated to enalapril 5 mg/day or matching placebo. Doses of enalapril (or matching placebo) were then doubled every two weeks to a maximum of 40 mg once daily (9 am) if no adverse effect occurred. After two months patients were readmitted, reassessed, and then they were started on the alternative treatment. Doses were again doubled every two weeks and patients were finally assessed after a further two months in the trial.

METHODS

Symptoms were evaluated by New York Heart Association score and by visual analogue scores for breathlessness, tiredness, and ankle swelling. Exercise capacity was measured by a modified Bruce protocol with stages which lasted three minutes. Left ventricular internal dimensions were derived from M mode echocardiography²⁷ and systolic time intervals from the aortic root echocardiogram.²⁸ Ambulatory electrocardiographic monitoring was performed for 48 hours with a Medilog-1 system and the results were expressed as events per 24 hours. Repetitive extrasystoles were defined as three or more consecutive ventricular extrasystoles. Blood pressure was measured with a Hawkesly random zero sphygmomanometer and heart rate was taken from the apex beat six hours after dosing.

Venous blood was drawn at 9 am, 24 hours after dosing from the patients who had fasted (apart from water), and remained supine overnight. Samples were assayed for serum electrolyte, urea, and creatinine concentrations, and for plasma concentrations of active renin²⁹ (normal range 10–50 μ U/ml), angiotensin II³⁰ (normal range 5–35

pmol/l), aldosterone³¹ (normal range 4–18 ng/dl (150–500 pmol/l)), vasopressin³² (normal range 0.3–0.7 pg/ml (0.3–0.6 pmol/l)), noradrenaline (normal range 0.8–3 nmol/l), and adrenaline (undetectable–0.2 nmol/l).³³

Total body potassium was derived from endogenous ^{40}K ³⁴ by means of a whole body counter, and total body sodium was similarly determined after neutron activation.^{35–37} Effective renal plasma flow³⁸ and glomerular filtration rates³⁹ were determined by single injection isotope techniques. Creatinine clearance was calculated from 24 hour urine collection and serum creatinine.

STATISTICAL ANALYSIS

Possible order and period effects or both were assessed by comparison of the differences between observations for the enalapril and placebo phases for the two groups by means of two sample *t* tests. In cases where the order effect was not significant we compared treatment effects by means of paired *t* tests on the enalapril and placebo measurements and ignored the order of treatment. Correlations were calculated by Pearson's product moment correlation coefficient and these were tested for significance by *t* tests. The data were log transformed where appropriate.

Results

In 17 patients the dose of enalapril was increased to a maximum of 40 mg/day, in two patients the dose was limited to 20 mg/day, and in one to 10 mg/day because of symptomatic hypotension, which also occurred in two patients on 40 mg/day. No severe hypotension was observed after the first dose in any patient. No patient failed to reach the maximum dose of placebo. Nineteen patients completed the study; one patient died suddenly during the placebo phase after showing an improvement in symptoms and exercise capacity on enalapril.

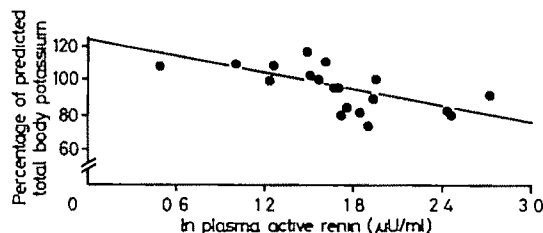


Fig Relation between total body potassium (expressed as a percentage of predicted normal) and log (ln) plasma active renin concentration ($r = -0.61$; $p < 0.01$).

BIOCHEMICAL VARIABLES

Hormone assays

At baseline and on placebo, mean plasma concentrations of active renin and angiotensin II were higher than normal but there was wide variation (Table 1). Plasma angiotensin II concentrations remained suppressed for 24 hours after the last dose of enalapril and there was a concomitant rise in plasma active renin concentration.

At baseline and during the placebo phase mean plasma concentrations of aldosterone, noradrenaline, and adrenaline were at the upper limit of normal and plasma vasopressin was raised; again values varied widely. Plasma concentrations of all these hormones, except adrenaline, fell during treatment with enalapril.

Electrolytes

At baseline and on placebo, mean serum potassium and magnesium were at the lower limit of normal and total body potassium was low at 96(13)% (mean (SD)) of predicted normal values. There was a significant increase in serum potassium and magnesium on enalapril. Total body potassium increased and total body sodium decreased, though neither change was statistically significant. There was no overall change in serum sodium. In two patients in whom postural hypotension developed (standing blood pressure on placebo 96/66 mm Hg and 108/88 mm Hg falling to 72/56 mm Hg and 68/44 mm Hg respectively on enalapril) serum sodium was reduced

on enalapril (from 139 to 134 mmol/l and from 134 to 121 mmol/l respectively). In two other patients, however, serum sodium rose on enalapril (from 129 to 133 mmol/l and from 134 to 137 mmol/l).

Total body potassium was negatively correlated with plasma active renin concentration measured at baseline ($r = -0.61$; $p < 0.01$) (Fig.). Changes in total body potassium ($r = 0.5$) and in total body sodium ($r = -0.21$) with enalapril were both related to initial plasma renin concentration though only the rise in total body potassium was statistically significantly related ($p < 0.05$).

Before treatment with enalapril plasma concentrations of the following hormones correlated significantly with plasma angiotensin II; active renin ($r = 0.90$; $p < 0.001$), aldosterone ($r = 0.57$; $p < 0.01$), vasopressin ($r = 0.49$; $p < 0.05$), and noradrenaline ($r = 0.66$; $p < 0.002$).

CLINICAL VARIABLES

Blood pressure and heart rate

Both systolic and diastolic blood pressure were significantly reduced on enalapril and heart rate also declined (Table 2).

Left ventricular function

Echocardiographic left ventricular systolic and diastolic dimensions were reduced by enalapril, although fractional shortening did not increase significantly (Table 2). The ratio of pre-ejection period to left ventricular ejection time was also

Table 2 Clinical variables measured at baseline, during enalapril treatment, and placebo treatment

	Baseline	Enalapril	Placebo	Significance*
Breathlessness (mm) (n = 19) mean (range)	56 (15-92)	24 (0-89)	45 (3-95)	
median	61	7	45	$p < 0.006$
Tiredness (mm) (n = 19) mean (range)	51 (0-100)	29 (0-88)	39 (0-96)	
median	58	13	41	NS
Systolic blood pressure (mm Hg) (n = 19)	117 (22)	100 (23)	121 (24)	$p < 0.00001$
Diastolic blood pressure (mm Hg) (n = 19)	75 (12)	62 (11)	72 (10)	$p < 0.001$
Heart rate (beats/min) (n = 18)	79 (12)	72 (9)	76 (10)	$p < 0.03$
Weight (kg) (n = 19)	66 (11)	67 (11)	67 (11)	NS
Glomerular filtration rate (ml/min) (n = 18)	70 (25)	58 (23)	71 (23)	$p < 0.00001$
Creatinine clearance (ml/min) (n = 17)	69 (29)	65 (24)	72 (23)	$p < 0.04$
Effective renal plasma flow (ml/min) (n = 15)	289 (101)	354 (128)	308 (119)	$p < 0.008$
Exercise time (min) (n = 19)	6.5 (3.2)	10.7 (2.4)	8.7 (3.1)	$p < 0.01$
LVEDD (cm) (n = 18)	6.9 (1.0)	6.6 (0.9)	6.9 (0.9)	$p < 0.004$
LVESD (cm) (n = 18)	5.8 (1.2)	5.4 (1.0)	5.8 (1.2)	$p < 0.003$
Fractional shortening (n = 18)	16 (7)	18 (7)	17 (6)	NS
PEP:LVET (n = 16)	667 (204)	534 (186)	631 (172)	$p < 0.03$
Ventricular extrasystoles (per 24 h) (n = 19)				
Mean	1702	1268	2140	
Median	555	560	659	
Range	15-11045	17-7827	17-9130	
Repetitive ventricular extrasystoles (per 24 h) (n = 19)				
Mean	4.6	3.9	4.7	
Median	1	1.5	1	
Range	0-41	0-35	0-58	

*Statistical significance of difference between enalapril and placebo. Values are mean (SD) unless otherwise stated. LVEDD, left ventricular end diastolic dimension; LVESD, left ventricular end systolic dimension; PEP:LVET, ratio of pre-ejection period to left ventricular ejection time.

reduced, indicating an improvement in ventricular function.

Ambulatory monitoring

Ventricular extrasystoles were significantly reduced (by 50%) during enalapril treatment, but the reduction in repetitive extrasystoles was not statistically significant.

Renal function

During enalapril treatment glomerular filtration rate measured isotopically was reduced and creatinine clearance also fell significantly, whereas effective renal plasma flow increased. The decline in glomerular filtration rate was reflected in a rise in serum urea and creatinine.

Exercise testing

Exercise performance improved on average by one treadmill stage during enalapril treatment.

Symptoms

New York Heart Association score improved (Table 3) during treatment with enalapril. Breathlessness and tiredness also improved but ankle swelling, not a prominent complaint at the start of the study, was unchanged.

ADVERSE EFFECTS

Weight increased in the first week on enalapril (0.4 (0.8) kg; $p < 0.05$) whereas there was no change after one week on placebo (-0.1 (0.6) kg). One patient had weight gain with increased ankle swelling; the latter improved on continued therapy without alteration of diuretic dose. Weight was similar on placebo and enalapril at the end of both two month periods.

Adverse responses included hypokalaemia (serum potassium < 3.5 mmol/l) in eight patients on placebo; slight increases in transaminases, one patient on placebo (alanine transaminase 62 U/l) and one on enalapril (60 U/l); and a pronounced increase in serum urea (6.8 mmol/l to 12.0 mmol/l) and creatinine (127 μ mol/l to 202 μ mol/l) in one patient on enalapril who also had postural hypotension (standing blood pressure on placebo 98/74 mm Hg and on enalapril 66/54 mm Hg). No patient developed proteinuria or a blood dyscrasia.

Other possible adverse effects were a mild persistent dry cough in one patient on enalapril. Transient skin eruptions were noted in three patients on enalapril (one case each of varicose eczema and two cases of a macular rash of hands or feet) and two on placebo (one case of varicose eczema and one of urticaria). In addition one patient developed thoracic herpes zoster during enalapril therapy from which

Table 3 New York Heart Association functional class at baseline, after treatment with enalapril, and on placebo. The difference between placebo and enalapril treatments was significant ($p < 0.05$) by a modified χ^2 test

Class	Baseline	Enalapril	Placebo*
4	2	0	2
3	14	3	9
2	4	15	8
1	0	2	0
Mean score	2.9	2.1	2.7

*One death.

she made an uncomplicated recovery. One patient who had previously had raised fasting blood glucose (8 mmol/l at baseline) developed glycosuria and a further increase in his fasting blood glucose on enalapril (placebo 11.9 mmol/l, enalapril 13.4 mmol/l) which he had received after placebo.

Discussion

The present trial has confirmed earlier reports of beneficial effects on exercise time and dyspnoea in patients with heart failure treated with the angiotensin converting enzyme inhibitors captopril²¹⁻²⁶ and enalapril. The degree of improvement in exercise performance was similar to that observed in other studies of enalapril but the placebo response in our study was also much greater than that reported in other studies.^{24, 25}

Our study design precludes any effect of patient training, allows within patient comparison of drug and placebo responses, and avoids difficulties in matching the baseline characteristics in placebo and active treatment groups which have affected other studies.²⁴ We saw no evidence of an order effect, indicating that the double blind treatment periods were long enough to exclude a carry over effect into placebo period, which would tend to cause drug action to be underestimated. Unlike the other two reported studies of enalapril regular diuretic therapy was unchanged in our patients.^{24, 25}

A single daily dose of enalapril was sufficient to sustain a reduction in angiotensin II and an increase in active renin over 24 hours. Mean plasma aldosterone, noradrenaline, and vasopressin concentrations were raised before angiotensin converting enzyme inhibition, and correlated significantly with angiotensin II concentration. When angiotensin II formation was inhibited concentrations of all of these hormones fell. This could have been the result of clinical improvement, but a reduction of the reported stimulatory effect of angiotensin II on sympathetic neuronal activity and on the secretion of vasopressin and aldosterone⁷ is more likely. A decrease in plasma noradrenaline has already been reported after both short^{16, 40} and long term^{16, 26} angiotensin converting enzyme inhibition in patients

with heart failure. We do not know of other reports of evidence of suppression of vasopressin secretion although such an effect is likely. Controlled studies of angiotensin converting enzyme inhibition in heart failure have consistently demonstrated long term suppression of plasma aldosterone^{26 41 42} perhaps caused by the counter regulatory effect of increased serum potassium concentration.⁴³ A fall of plasma aldosterone could be important in maintaining sodium balance as blood pressure and glomerular filtration rate fall. Reduction in sympathetic activity and of plasma vasopressin concentrations may result in additional arterial and venous dilatation^{43 44}; the latter is likely to promote excretion of water.¹³

We found that serum potassium and magnesium concentrations rose on enalapril, and this effect may have been largely a result of a related fall in plasma aldosterone. In contrast to our earlier study with captopril,²⁶ the rise in mean total body potassium on enalapril was not statistically significant. The increase of body potassium on enalapril was directly related to the baseline plasma renin. Moreover, the extent of initial potassium depletion is related to plasma renin.⁴⁵ Thus increases in total body potassium with angiotensin converting enzyme inhibition might be expected only in patients who are already potassium depleted. Transient weight gain, which we have also observed with captopril,²⁶ occurred in the first week of enalapril therapy. This was probably largely due to a fall in blood pressure and possible renal dysfunction.⁴⁶ In the long term weight was unchanged, suggesting that there may have been a secondary diuresis probably aided by the falls in plasma aldosterone and vasopressin. We observed no long term changes in mean serum sodium or total body sodium. There was a significant reduction in ventricular extrasystoles during enalapril treatment, probably partly reflecting the increases in serum potassium and magnesium, the reduction in sympathetic activity, and the reduced cardiac dimensions. Several studies have shown that frequent ventricular extrasystoles indicate a poor prognosis in heart failure,^{47 48} and sudden death, presumably from arrhythmias, is common in patients with left ventricular failure.⁴⁹ If a causal relation does exist this is one mechanism whereby angiotensin converting enzyme inhibitors might reduce mortality.

As we had expected on theoretical grounds²⁰ and from earlier experience²⁶ enalapril treatment, although it increased renal blood flow, led to a fall in both creatinine clearance and in glomerular filtration rate measured isotopically and an increase in serum urea and creatinine concentrations. These changes represent the loss of a beneficial direct intrarenal action of angiotensin II. In cardiac failure enhanced angiotensin II mediated constriction of the efferent

glomerular arterioles^{18 20} probably helps to sustain glomerular filtration. Blood is also diverted to the large juxtamedullary glomeruli which have long loops of Henle that descend deep into the renal medulla accompanied by vasa recta.^{50 51} Angiotensin II mediated increased tone in the vasa recta may improve counter current exchange in the renal medulla and thus sustain urea excretion.¹⁹ Reduction of intrarenal angiotensin II by angiotensin converting enzyme inhibition would lead to loss of these various compensatory effects and thus to a fall in glomerular filtration rate and a rise in serum urea concentration. Only in very severe cardiac failure, in which gross excess of intrarenal angiotensin II causes preglomerular arteriolar constriction,^{19 52 53} hyponatraemia, and rapidly advancing azotaemia, are angiotensin converting inhibitors likely to improve renal function.

Reduction in heart rate is to be expected with angiotensin converting enzyme inhibition in cardiac failure despite dilatation of resistance vessels and probably results from a combination of venous dilatation, reduced sympathetic tone,^{16 45} and loss of the vagolytic effect of angiotensin II.^{15 17} Although in the long term the reduction in blood pressure was generally well tolerated, initiation of treatment with captopril^{54 55} or enalapril⁵⁶ may be associated with severe hypotension, bradycardia, and syncope. For this reason such treatment must be started under close supervision.

In response to the presumed reduction in preload and afterload^{57 58} we observed a reduction in left ventricular dimensions. An improvement in systolic function is suggested by the improvement in the ratio of pre-ejection period to left ventricular ejection time which has been shown to correlate with left ventricular fraction.²⁸ The reduction in end diastolic dimension implies a reduction in filling pressure.

Apart from postural hypotension which caused symptoms in three patients, adverse reactions seemed to be no more common with enalapril than with placebo. Although very low ambulant pressures without symptoms seem to be tolerated by many patients, an excessive fall below renal autoregulatory thresholds may have accounted for the pronounced increase in serum creatinine associated with hypotension and hyponatraemia in one patient. The patient who developed diabetes did so at the end of the four months of study and had had raised fasting blood glucose concentrations before joining the study. Impaired glucose metabolism does not seem to be a feature of angiotensin converting enzyme inhibition,⁵⁹ however, in one study blood glucose concentration was not included in the coronary risk factors studied.⁶⁰

Despite the minor consequent impairment of renal

function and occasional hypotension, angiotensin converting enzyme inhibitors clearly improve symptoms in heart failure. The reduction of ventricular arrhythmias moreover offers the distinct hope that these drugs may help to prolong survival in patients with cardiac failure.

Dr J G F Cleland is supported by a training fellowship from the Medical Research Council and Dr S G Ball by the British Heart Foundation.

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Acute haemodynamic and metabolic effects of dopexamine, a new dopaminergic receptor agonist, in patients with chronic heart failure

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SUMMARY Dopexamine, a new compound with postjunctional dopamine receptor activating and beta adrenoceptor agonist properties, was given to 10 patients with chronic heart failure at diagnostic cardiac catheterisation to investigate its acute haemodynamic and metabolic effects. The drug was administered by intravenous infusion in three incremental doses and produced significant dose related increases in cardiac index, stroke volume index, and heart rate and falls in systemic vascular resistance and left ventricular end diastolic pressure; aortic and pulmonary artery pressures were unchanged. Isovolumic phase (max dP/dt and KVmax) and ejection phase (peak aortic blood velocity, maximum acceleration of blood, and maximum rate of change of power with time during ejection) indices of myocardial contractility were all increased by dopexamine but these changes were hard to interpret in the presence of an increase in heart rate. Myocardial efficiency and ejection fraction were both increased and left ventricular end diastolic and end systolic volumes fell. These largely beneficial changes were achieved without a statistically significant increase in myocardial oxygen consumption or disturbance of myocardial metabolic function. Dopexamine was well tolerated but tremor was reported by two patients at the intermediate dose and mild chest pain by two patients at the high dose.

Dopamine is well established in the management of acute or acute on chronic heart failure.^{1,2} The clinical value of dopamine, however, is often limited by alpha adrenoceptor mediated peripheral constriction,^{3,4} which increases the load faced by the left ventricle during ejection. Consequently myocardial oxygen demand increases and myocardial ischaemia may be induced in patients with coronary artery disease.⁵

Dopexamine (Fisons Pharmaceutical Division) is a recently synthesised compound which is structurally related to dopamine (Fig. 1). Like dopamine it can only be administered intravenously. In vitro and in vivo animal experiments show that the drug activates postjunctional dopamine receptors (equipotently with dopamine), has substantial beta₂ adrenoceptor agonist activity, has no beta₁ adrenoceptor agonist activity, and, unlike dopamine, is inactive at

the alpha adrenoceptors.^{6,7} This pharmacological profile suggests that dopexamine will produce haemodynamic improvement in patients with heart failure and because of its theoretical superiority to dopamine is worthy of evaluation. The haemodynamic and metabolic effects of dopexamine were evaluated in 10 patients with severe chronic heart failure.

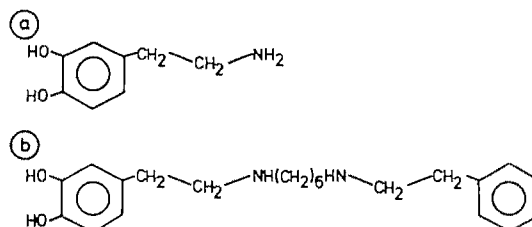


Fig 1 Chemical structure of dopamine (a) and dopexamine (b).

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Accepted for publication 21 May 1985

Patients and methods

PATIENTS

Ten patients (nine men and one woman, mean age 54 (range 44–69)) with chronic heart failure undergoing diagnostic cardiac catheterisation participated in the study. Each patient gave written consent and the study protocol was approved by the hospital ethics committee. All patients were severely limited by dyspnoea (class 3, New York Heart Association), had radiographic evidence of cardiomegaly and pulmonary venous congestion, and required large maintenance doses of diuretics. Five patients were in sinus rhythm and five had atrial fibrillation. Heart failure was due to dilated cardiomyopathy in four patients, coronary artery disease in five patients, and in one patient it was associated with poor left ventricular function after mitral valve replacement (the mitral prosthesis was found to be functioning normally).

INSTRUMENTATION

Patients were studied after an overnight fast. One hour before catheterisation, diazepam (10 mg) was given intramuscularly and at the same time heparin (45 units/kg) was given intravenously to minimise the effect of a subsequent dose of heparin upon free fatty acid concentrations.⁸ Right atrial and pulmonary artery pressures were measured by means of a fluid filled coaxial catheter system from the right femoral vein. Cardiac output was measured in triplicate by the indocyanine green dye dilution method and an earpiece densitometer (Nihon Kohden MLC 4100).⁹ The coronary sinus was cannulated with a Ganz catheter (Wilton Webster Inc) from a left antecubital vein and its position was confirmed by the injection of contrast medium. This allowed coronary sinus blood to be sampled and coronary sinus flow to be measured. The long sheath technique¹⁰ was used to position a Millar multisensor catheter from the right femoral artery in the left heart for the measurement of high fidelity left ventricular and aortic pressures and aortic blood velocity. A pigtail catheter from the left femoral artery was positioned in the left ventricle for blood sampling and injection of contrast medium. The sternal angle was used as the zero reference point for pressure measurements. The electrocardiogram (standard lead II) was monitored throughout the study period.

PROTOCOL

Routine treatment for heart failure was not given to patients on the morning of the study. Conventional right and left heart catheterisation was performed. Another dose of heparin (45 units/kg) was given immediately after arterial catheterisation. Mea-

surements were made of pressure, and coronary arteriography and left ventricular cineangiography (right anterior oblique projection) were performed. After this initial diagnostic procedure the patient's haemodynamic state was allowed to stabilise for 20 minutes before the start of the study. During the study period right atrial, pulmonary artery, left ventricular, and aortic pressures, and cardiac output and aortic blood velocity were measured simultaneously, and left ventricular and coronary sinus blood was sampled. Dopexamine was administered by continuous intravenous infusion. The dose was increased at intervals of 10 minutes. The doses of 1, 3, and 6 $\mu\text{g/kg/min}$ are described as low, intermediate, and high doses respectively. Measurements were made during an initial control period and five minutes after each dose increment. After we had completed measurements at the highest dose of the drug tolerated by each patient we performed a second left ventricular cineangiogram during drug infusion.

DATA ANALYSIS

Pressure signals, the aortic blood velocity signal, and the electrocardiogram were displayed on a twelve channel Cambridge recorder. Recordings of 18 seconds duration were selected and converted to digital form by computer (Varian 600E) and then stored on disc for subsequent off line editing and analysis. The high fidelity left ventricular pressure records were used to derive the isovolumic phase indices of myocardial contractility: dP/dt ,¹¹ the maximum rate of pressure increase with time; and KVmax ,¹² the product of the series elastic stiffness constant and the velocity of contractile element shortening at zero load. The aortic velocity signal was used to derive the ejection phase indices of myocardial contractility: peak aortic blood velocity,¹³ and maximal acceleration of blood during ejection.¹⁴ The aortic velocity signal was converted to volumetric flow by multiplication by the aortic cross sectional area, which had been determined by echocardiography. This flow signal was then calibrated in vivo by setting the signal of the stroke volume to equal that of the stroke volume derived from simultaneously performed indocyanine green dye measurements. Maximum rate of change of power with time (dPower/dt)¹⁵ was determined from the first derivative of the product of instantaneous aortic pressure and flow. Cardiac index, stroke volume index, and systemic and pulmonary vascular resistances were calculated from standard formulas.

Blood oxygen content was measured by a LEX 02 CON-TL. Left ventricular and coronary sinus blood samples were analysed for concentrations of lactate and pyruvate,¹⁶ hydroxybutyrate and aceto-

acetate,¹⁷ glycerol,¹⁸ free fatty acids,¹⁹ and glucose. The extraction ratio of a substrate is defined as the difference between the arterial and coronary sinus concentration of that substrate expressed as a percentage of the arterial concentration of the substrate. Coronary sinus blood flow was measured by continuous thermodilution.²⁰ Myocardial oxygen consumption was calculated as the product of coronary sinus flow and the arterial coronary sinus oxygen difference. Myocardial efficiency, relating the external work performed by the left ventricle (left ventricular minute work) to myocardial oxygen consumption, was estimated according to the formula of Bing and Michal.²¹

Left ventricular cineangiograms were analysed by a computer light pen system to give left ventricular volumes and ejection fraction.

STATISTICAL ANALYSIS

Results are expressed as means (SEM). Analysis of variance was used to test for treatment effect. If this was significant ($p < 0.05$) for a particular variable then the least significant difference method²² was used to determine the significance of differences between control and the three doses and among the three doses.

Results

HAEMODYNAMICS

The data for measured and calculated haemodynamic variables are shown in Table 1 and in Fig. 2. When variables were significantly changed by dopexamine from their control value, the magnitude of the change was found to be dose related. Heart rate was increased from a control value of 90(5) beats/min to 120(6) beats/min at the high dose (33%, $p < 0.001$). Cardiac index rose in all patients from a control mean of 1.4(0.1) l/min/m² to 3.1(0.4) l/min/m² at the high dose (121%, $p < 0.001$). Stroke volume index increased from a mean of 16(2) ml/beat/m² to 26(4) ml/beat/m² at the high dose

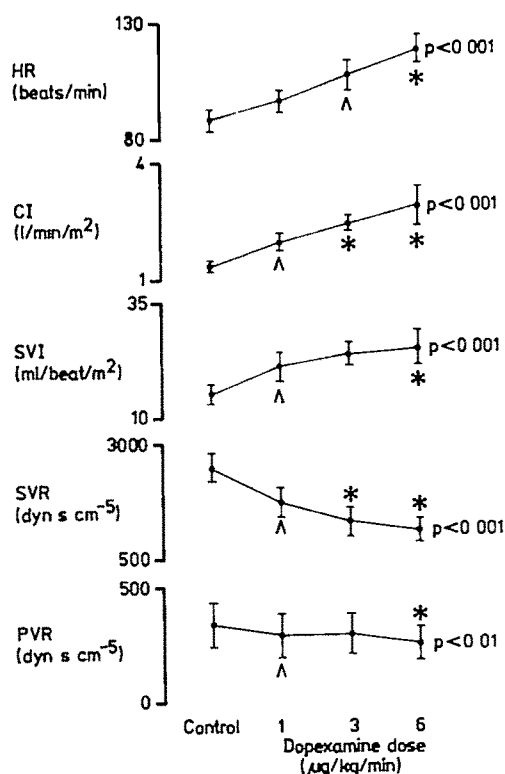


Fig. 2 Effect of treatment with three incremental doses of dopexamine on heart rate (HR), cardiac index (CI), stroke volume index (SVI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). Significance of the treatment effect is shown. The arrow indicates the first dose at which a change from control was significant ($p < 0.05$). Asterisks indicate when the effect of the dose was significantly different from the effect of a preceding dose ($p < 0.05$).

(63%, $p < 0.001$). Both aortic and pulmonary artery pressures were essentially unchanged by dopexamine administration and therefore, because flow was increased, calculated systemic and pulmonary

Table 1 Effects (mean (SE)) of an intravenous infusion of dopexamine at three incremental doses on aortic pressure (AP), pulmonary artery pressure (PAP), left ventricular end diastolic pressure (LVEDP), and mean right atrial pressure (RA)

	Control (n = 10)	Dopexamine dose 1 µg/kg/min (n = 10)	3 µg/kg/min (n = 10)	6 µg/kg/min (n = 8)	Significance*
AP (mm Hg):					
Systolic	90 (3)	92 (3)	89 (3)	91 (3)	NS
Diastolic	64 (4)	63 (4)	59 (4)	60 (4)	NS
Mean	76 (4)	76 (3)	73 (4)	73 (3)	NS
PAP (mm Hg):					
Systolic	41 (4)	42 (4)	42 (5)	45 (5)	NS
Diastolic	22 (3)	21 (2)	19 (5)	20 (4)	NS
Mean	30 (3)	30 (3)	29 (4)	31 (4)	NS
LVEDP (mm Hg)	23 (3)	20 (3)	17 (3)	18 (3)	$p < 0.01$
RA (mm Hg)	6 (2)	5 (2)	4 (2)	4.5 (2)	$p < 0.05$

*Statistical significance of treatment effect NS, not significant.

vascular resistance were both reduced from 2360(277) dyn s cm⁻⁵ to 1204(267) dyn s cm⁻⁵ ($p < 0.001$) and from 339(99) dyn s cm⁻⁵ to 261(82) dyn s cm⁻⁵ ($p < 0.01$) respectively.

There were small reductions in both right and left heart filling pressures. Left ventricular end diastolic pressure was 23(3) mm Hg at control and fell to 18(3) mm Hg at the high dose. Mean right atrial pressure fell from 6(2) mm Hg to 4.5(2) mm Hg ($p < 0.05$).

Left ventricular end diastolic and end systolic volume were both reduced by dopexamine from 388(33) cm³ to 279(25) cm³ ($p < 0.05$) and from 272(29) cm³ to 195(23) cm³ ($p < 0.05$) respectively. Ejection fraction was increased from 20(3) % to 30(3) % ($p < 0.05$).

INDICES OF CONTRACTILITY

The data for the various indices of contractility are shown in Fig. 3. The two isovolumic phase indices of myocardial contractility were both significantly increased during dopexamine infusion. dP/dt max rose from 646(50) mm Hg/s at control to 847(86) mm Hg/s at the high dose ($p < 0.001$). Similarly KVmax was increased from 65(4)s to 88(12)s ($p < 0.01$).

Technically satisfactory velocity signals were obtained in seven of the 10 patients studied. The ejection phase indices of contractility were all significantly increased by dopexamine administration ($p < 0.01$). Peak aortic blood velocity increased from a control value of 30(5) cm/s to 58(13) cm/s at the high dose level. Maximum acceleration of blood during ejection rose from 520(123) cm/s² to 965(257) cm/s². The maximum rate of change of power with time (dPower/dt) was increased from 38(7) watts/s to 72(13) watts/s at the high dose.

Fig. 4 illustrates the relation between two of these indices of contractility (max dP/dt and KVmax) and changes in heart rate. In only one patient at the low and intermediate dose levels was max dP/dt increased without concomitantly large increase in heart rate. KVmax was increased in four patients at the low dose level and in two of these four patients at the intermediate dose level without concomitantly large increase in heart rate.

CORONARY HAEMODYNAMICS AND MYOCARDIAL METABOLIC RESPONSES

The coronary sinus was successfully cannulated in eight of the 10 patients. The data for coronary haemodynamics and myocardial metabolic responses are shown in Tables 2 and 3. Dopexamine produced small statistically insignificant increases in coronary sinus flow and myocardial oxygen consumption and increased myocardial efficiency from 7(3)% at control to 12(4)% at the high dose level ($p < 0.01$).

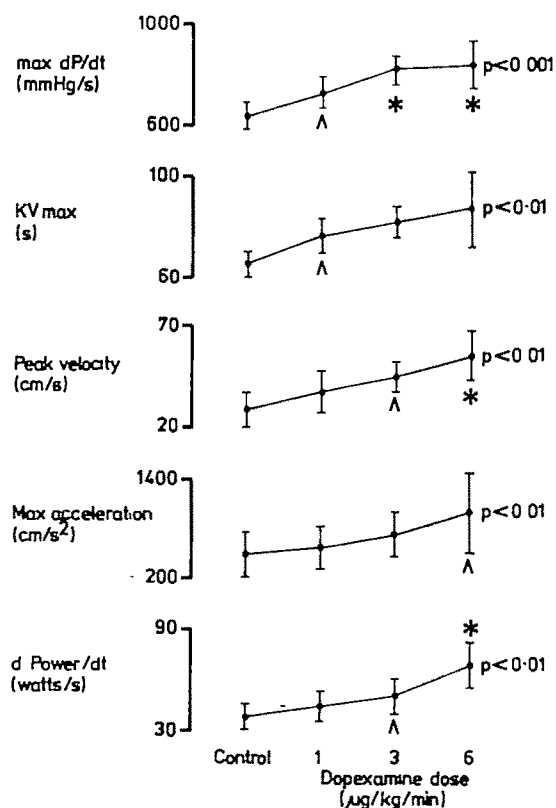


Fig. 3 Effect of treatment with three incremental doses of dopexamine on maximum dP/dt, KVmax, peak aortic blood velocity, maximum acceleration of blood during ejection, and dPower/dt. Significance of the treatment effect is shown. The arrow head indicates the first dose at which a change from control was significant ($p < 0.05$). Asterisks indicate when the effect of the dose was significantly different from the effect of a preceding dose ($p < 0.05$).

In the total group the arterial concentrations of lactate, pyruvate, ketone bodies, and glucose did not change appreciably with dopexamine administration but there was a significant increase in the arterial concentrations of glycerol and free fatty acids ($p < 0.05$). Dopexamine reduced the myocardial extraction of most substrates but this change was significant ($p < 0.05$) for free fatty acids only. During the control period two patients (one with coronary artery disease and one with congestive cardiomyopathy) were net myocardial producers of lactate. During dopexamine infusion the patient with coronary artery disease continued to produce lactate and another patient with coronary artery disease switched from being a net myocardial extractor of lactate to being a net producer of lactate, suggesting a change to anaerobic metabolism. The patient with

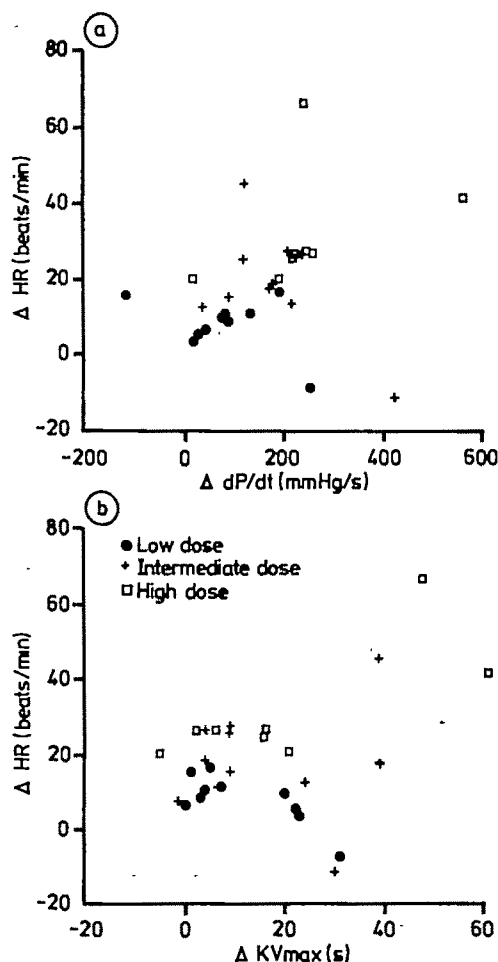


Fig. 4 Relation between change in heart rate and change in max dP/dt (a) and change in KVmax (b) in individual patients at low ($1 \mu\text{g/kg/min}$), intermediate ($3 \mu\text{g/kg/min}$), and high ($6 \mu\text{g/kg/min}$) doses.

congestive cardiomyopathy became a net extractor of lactate during dopexamine infusion but another patient with congestive cardiomyopathy changed from being a net extractor of lactate to being a net producer of lactate during dopexamine infusion.

ADVERSE REACTIONS

The low ($1 \mu\text{g/kg/min}$) dose was well tolerated by all patients. At the intermediate ($3 \mu\text{g/kg/min}$) dose two patients reported the symptom of tremulousness at a time when both had pronounced haemodynamic responses. Therefore we did not give these two patients the high ($6 \mu\text{g/kg/min}$) dose. Of the eight patients who were given the high dose, two patients (both with severe coronary artery disease) reported

mild chest pain typical of angina pectoris but which did not interfere with data collection and which resolved rapidly after discontinuation of the drug. No arrhythmias were detected during the study.

Discussion

The aim of this study was to evaluate the acute effects of an intravenous infusion of dopexamine on haemodynamics and myocardial metabolic function in patients with chronic heart failure. The basal low values for cardiac index, stroke volume index, and ejection fraction and the high values for systemic vascular resistance and ventricular volumes testify to the severity of heart failure in the study group. The results of the study indicate that the drug has powerful dose related effects; principally to increase cardiac index (maximum increase 121%) and stroke volume index (maximum increase 63%), and to reduce systemic vascular resistance (maximum reduction 49%) without altering pulmonary or aortic pressures. These changes, which are beneficial in patients with heart failure, occurred without a significant increase in myocardial oxygen consumption or alteration of myocardial metabolic function.

The pronounced reduction in systemic vascular resistance produced by dopexamine suggests that the drug has profound vasodilator properties; this accords with its postjunctional dopamine receptor stimulating and β_2 adrenoceptor agonist actions. Our results give no indication of the vascular beds on which the drug has its principal action, but the large number of postjunctional dopaminergic receptors in the renal vascular bed and their relative paucity in the femoral vascular bed suggest that much of the increased cardiac output may be directed to the kidneys. The small reductions observed in right and left ventricular filling pressures and pulmonary vascular resistance suggest that dopexamine has relatively little action on systemic capacitance vessels or on the pulmonary circulation and that its principal site of vasodilator action is the systemic arterial system (that is reduction of afterload).

Although all of the isovolumic and ejection phase indices of myocardial contractility were significantly increased by dopexamine, these findings must be interpreted with caution. The contractile state of the ventricle is modulated by preload, afterload, and heart rate.²³ All of these changed during the study and such changes may therefore have been responsible for the apparent increase in the level of myocardial contractility. It is instructive to compare the results of this study with those of a previous study performed in our laboratory on the haemodynamic effects of the vasodilator sodium nitro-

Table 2 Effects (mean (SE)) of an intravenous infusion of dopexamine at three incremental doses on coronary sinus flow (CSF), myocardial oxygen consumption (MVO₂), left ventricular minute work (LVMW), and myocardial efficiency

	Control (n = 8)	Dopexamine dose 1 µg/kg/min (n = 8)	3 µg/kg/min (n = 8)	6 µg/kg/min (n = 6)	Significance*
CSF (ml/min)	173 (50)	198 (64)	173 (41)	229 (56)	NS
MVO ₂ (ml/min)	22 (7)	26 (9)	21 (5)	29 (10)	NS
LVMW (kg/m/min)	1.6 (0.7)	2.4 (1)	3 (0.9)	4.1 (1.2)	p < 0.001
Efficiency (%)	7 (3)	7 (2)	9 (4)	12 (4)	p < 0.01

*Statistical significance of treatment effect. NS, not significant.

prusside in a similar group of patients with chronic heart failure.²⁴ Sodium nitroprusside produced changes in preload and afterload which resembled those produced by dopexamine, but in contrast heart rate was not altered and the isovolumic phase indices of contractility maximum dP/dt and KVmax were unchanged. It could be argued that the increase in the indices of contractility observed in our patients treated with dopexamine were secondary to an increase in heart rate. Analysis of individual responses which compared changes in heart rate with changes in the isovolumic phase indices seems to confirm this assertion with respect to maximum dP/dt (Fig. 4). There were several patients, however, in whom KVmax rose substantially at the low and intermediate doses without concomitant increases in heart rate (Fig. 4), a finding that may cautiously be interpreted as evidence that dopexamine has some direct positive inotropic action.

The striking increases in cardiac output observed in all patients were mediated through both an increase in stroke volume and an increase in heart rate. Inspection of Fig. 2 suggests that at the low dose the effect of a stroke volume increase predominated but at the intermediate and high doses increased heart rate was an important contributory factor to the improvement in cardiac output. The increase in heart rate produced by dopexamine may be due either to a direct positive chronotropic action

(beta, adrenoceptor mediated) or to a reflex tachycardia secondary to peripheral vasodilatation caused by the drug. We suggest that it is the former because when the "pure" vasodilator sodium nitroprusside was given to patients with heart failure there was a similar fall in systemic vascular resistance to that produced by dopexamine without a significant alteration in heart rate.²⁴ Administration of a drug with a positive chronotropic action to patients with coronary artery disease is potentially deleterious because myocardial ischaemia may be induced either by increased myocardial oxygen consumption²⁵ or by a reduction in coronary artery diastolic filling time.

The highly significant haemodynamic changes observed in our patients were associated with only a small and statistically insignificant rise in myocardial oxygen consumption. Myocardial oxygen consumption is determined by heart rate, the contractile state of the ventricle, and ventricular load.²⁵ In our patients the positive chronotropic and possible positive inotropic effects of dopexamine would both be expected to increase myocardial oxygen consumption, but this effect has in the main been offset by other drug induced reductions in components of left ventricular load such as systemic vascular resistance and left ventricular volume and end diastolic pressure.

The effect of dopexamine on myocardial energetics can be examined by estimating myocardial

Table 3 Summary of metabolic results (mean (SE))

Substance	Control			Dopexamine dose 1 µg/kg/min			3 µg/kg/min			6 µg/kg/min		
	A (mol/l)	A-V (mol/l)	ER (%)	A (mol/l)	A-V (mol/l)	ER (%)	A (mol/l)	A-V (mol/l)	ER (%)	A (mol/l)	A-V (mol/l)	ER (%)
Lactate	0.69 (0.11)	0.09 (0.03)	12 (7.4)	0.67 (0.1)	0.07 (0.02)	14.8 (4.4)	0.72 (0.11)	0.06 (0.04)	9 (5.6)	0.87 (0.14)	0.005 (0.04)	1.05 (5.4)
Pyruvate	0.05 (0.01)	0.002 (0.003)	-4.9 (16.5)	0.04 (0.01)	0.001 (0.004)	-2.1 (13.7)	0.046 (0.007)	0.001 (0.004)	-4.9 (11.2)	0.052 (0.01)	0.005 (0.007)	-2.6 (11.2)
Hydroxybutyrate	0.42 (0.07)	0.14 (0.02)	32.9 (2.0)	0.42 (0.08)	0.14 (0.03)	29.9 (3.6)	0.51 (0.11)	0.13 (0.03)	23.2 (4.6)	0.49 (0.18)	0.1 (0.04)	20 (10.4)
Acetoacetate	0.19 (0.02)	0.09 (0.01)	43.3 (6.6)	0.18 (0.02)	0.07 (0.02)	37.3 (6.2)	0.18 (0.02)	0.07 (0.01)	39.9 (5.2)	0.18 (0.04)	0.07 (0.02)	37.9 (5.2)
Glycerol	0.14 (0.02)	0.02 (0.007)	14.1 (5.0)	0.18 (0.03)	0.01 (0.01)	3.6 (8.4)	0.21 (0.03)	0.03 (0.01)	15.4 (6.2)	0.22* (0.04)	-0.03 (0.02)	-18.8 (14.4)
Free fatty acids	0.86 (0.08)	0.15 (0.02)	17.1 (2.9)	1.01 (0.09)	0.12 (0.07)	9.7 (6.5)	1.19* (0.13)	0.14 (0.07)	8.9 (5.9)	1.3* (0.13)	-0.01 (0.09)	-1.2* (6.6)
Glucose	6.2 (0.3)	0.07 (0.08)	1.1 (1.4)	6.1 (0.3)	0.11 (0.13)	1.7 (2.2)	6.4 (0.3)	0.36 (0.13)	5.2 (1.8)	6.6 (0.3)	0.44 (0.22)	3.7 (1.8)

A, arterial concentration; A-V, arteriovenous concentration difference; ER, extraction ratio. *Significantly different from control value (p < 0.05).

efficiency, which relates the external work performed by the ventricle to myocardial oxygen consumption. In a normal heart myocardial efficiency is approximately 40%.^{21,26} The very low basal value of 7% emphasises the severity of disturbance of myocardial energetics in our patients. Dopexamine significantly increased myocardial efficiency ($p < 0.01$) principally by an increase in external work performed by the left ventricle, since myocardial oxygen consumption was essentially unchanged. External work is determined by the extent of muscle shortening against load and therefore it can be inferred that many of the beneficial effects of dopexamine are due to favourable alterations in ventricular loading.

In most patients the pattern of myocardial substrate utilisation when control measurements were obtained was similar to results reported in the normal heart,²⁷ but two patients (one with coronary artery disease and one with congestive cardiomyopathy) were net myocardial producers of lactate at rest and this indicates some degree of anaerobic metabolism. Dopexamine seemed to have no important actions on myocardial metabolic function; it had little effect on arterial concentrations, extraction, and extraction ratios of most of the substrates measured. The small increase in the arterial concentration of free fatty acids is probably related to both the lipoprotein lipase activating action of heparin²⁸ and the effect of fasting before and during the study. The reduction in the extraction ratio of free fatty acids is difficult to interpret. It may be spurious, because the free fatty acid arteriovenous concentration difference was narrow, and therefore small errors in measuring concentrations would have had a large effect upon estimated extraction.

Dopexamine was well tolerated by the patients in this study and no arrhythmias were seen. Two patients reported tremor. This symptom has been described in similar groups of patients treated with beta adrenergic agonist drugs.^{29,30} At the high dose level two of the patients with severe coronary artery disease experienced mild chest pain typical of angina pectoris at a time when both had substantial increases in heart rate ($> 30\%$). One of these patients was a net myocardial producer of lactate at rest (extraction ratio -23%) and remained so at the high dose (extraction ratio -6%). The second patient was a myocardial extractor of lactate at rest, and the onset of chest pain was associated with evidence suggesting a switch to anaerobic myocardial metabolism (extraction ratio -12%). In neither of these two patients was the increase in myocardial oxygen consumption (4.7 and 2.3 ml/min) at the high dose greater than in the group mean (6.5 ml/min) nor was the onset of chest pain associated with the development of electrocardiographic manifestations of

myocardial ischaemia.

The study results indicate that dopexamine has many beneficial haemodynamic properties in patients with heart failure, although its positive chronotropic action may limit its use in patients with coronary artery disease in whom the relation between myocardial supply and demand may be precarious. The precise mode of action of the drug is uncertain but improved cardiac performance is probably due principally to its peripheral vasodilator properties, although it may also have a positive inotropic effect. Further clinical evaluation is required, particularly an assessment of the efficacy of dopexamine in the setting of acute pump failure and a direct comparison of its actions with those of dopamine.

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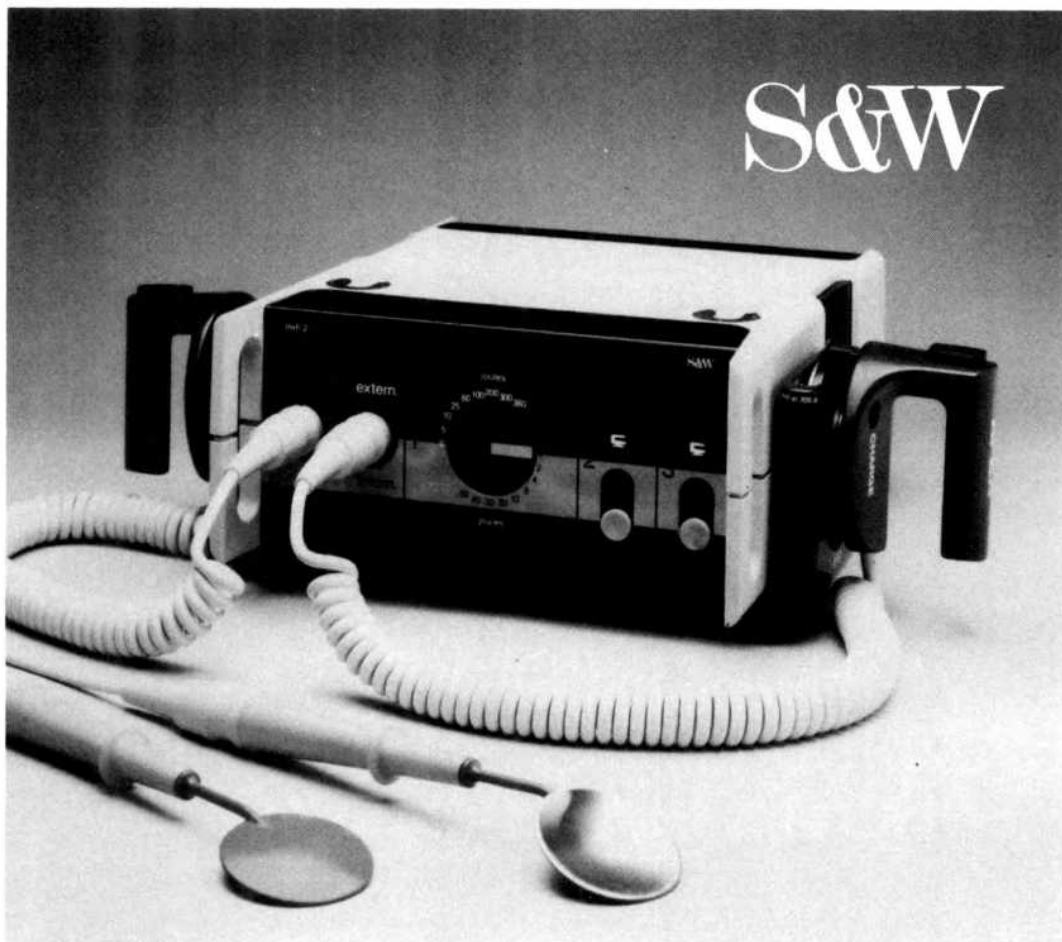
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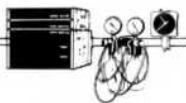
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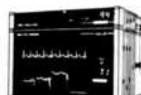
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Respiratory gas exchange in the assessment of patients with impaired ventricular function

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SUMMARY Respiratory gas exchange on exercise was evaluated as a non-invasive method of assessing patients with heart failure. Twenty four men (age 28-72) with symptomatic chronic stable heart failure (New York Heart Association class II-III) and ten controls aged 36-70 were studied. During treadmill exercise oxygen consumption and carbon dioxide production were measured continuously by analysis of mixed expired gas with a computerised mass spectrometer. The anaerobic threshold was defined as the oxygen consumption at which carbon dioxide production increased disproportionately in relation to oxygen consumption.

Oxygen consumption was stable at rest and increased on exercise, reaching a steady state within three minutes of any change in workload. The measurements of maximum oxygen consumption at the end of exercise and of anaerobic threshold were reproducible (retest reliability coefficients 90% and 91% respectively). There were significant differences in maximum oxygen consumption between functional classes. Similarly, there were significant differences in anaerobic threshold between classes, though there was considerable overlap.

Measurement of oxygen consumption and anaerobic threshold provides an objective non-invasive assessment of patients with heart failure.

The physiological stress of exercise has been widely used to evaluate the symptoms and cardiac function of patients with heart disease.¹⁻⁴ It should be possible to assess the severity of heart disease and determine functional capacity by measuring a patient's response to exercise. Left ventricular function at rest as assessed by angiocardigraphy, echocardiography, or radionuclide techniques correlates poorly with functional class.⁴ Exercise haemodynamic monitoring is invasive and is not without risk.⁵ Furthermore haemodynamic variables measured at rest or on exercise do not relate closely to exercise capacity in patients with severe heart failure.^{2,6}

Recently, impaired cardiac function has been assessed by measuring oxygen consumption during exercise.^{3,4,6-8} Patients with congestive cardiac failure have a reduced maximum aerobic exercise capacity because of inadequate transport of oxygen to

working skeletal muscle.⁷ Lactic acid is generated by anaerobic metabolism in skeletal muscle. Buffering of lactic acid by bicarbonate generates carbon dioxide in excess of that resulting from oxidative metabolism. An aerobic-anaerobic threshold was first postulated over 20 years ago,⁹ and is thought to be reflected by a sharp increase in plasma lactate. Measurement of anaerobic threshold has been proposed as an objective means of assessing aerobic capacity.¹⁰⁻¹³ The clinical importance of such a measurement in cardiac patients is less certain. We used a mass spectrometer linked to a computer to analyse mixed expired air and thus determine maximum oxygen consumption and anaerobic threshold in patients with cardiac failure. We investigated the reproducibility of the test and the relation of oxygen consumption and anaerobic threshold to the severity of heart failure.

Patients and methods

We studied patients who had had stable symptomatic heart failure for more than three months with exercise intolerance due to dyspnoea, fatigue, or

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Accepted for publication 10 June 1985

aching legs. In addition patients had cardiomegaly, defined as a cardiothoracic ratio $>55\%$ on chest radiograph, and left ventricular ejection fraction $\leq 45\%$ on radionuclide angiography or echocardiographic study. Twenty four men (mean age was 50 years, range 28–72) entered the study. The cause of heart failure was coronary artery disease in 15, dilated cardiomyopathy in six, hypertensive heart disease in two, and valvar regurgitation in one. Individual drug therapy was recorded. Patients with myocardial infarction during the previous six months, evidence of myocardial ischaemia or ventricular arrhythmias on exercise testing, obstructive valvar heart disease, pulmonary disease (documented by pulmonary function tests), or an inability to exercise for any reason other than dyspnoea or fatigue were excluded from the study.

Ten men (mean age 48 years, range 36–70) who were free of heart disease on the basis of history, physical examination, and 12 lead electrocardiogram were also studied. All patients and controls gave written consent to the study.

Functional class was assessed by modified criteria of the New York Heart Association¹⁴: (I) No undue symptoms on strenuous exercise; (II) able to walk indefinitely without slowing pace and (a) climb two flights of stairs or (b) unable to climb two flights of stairs; (III) walk at a reduced pace on the flat (a) indefinitely at a reduced rate or (b) have to stop; (IV) symptoms at rest. Functional class was also assessed by a specific activity scale (1981).¹⁵ Patients were asked to fill in a standardised questionnaire on their symptoms.

EXERCISE TEST

All patients underwent at least three exercise tests over two to 14 days. In 10 patients four exercise tests were performed. Patients exercised three hours after a light meal, at the same time of day, and three hours after a last dose of any vasodilator therapy.

Each patient underwent progressive treadmill exercise testing which followed a heart failure protocol (stage 1, 1 mph (1.6 km/h) with 0% gradient; stage 2, 1.5 mph (2.4 km/h) with 0% gradient; stage 3, 2 mph (3.2 km/h) with 0% gradient; stage 4, 2.5 mph (4 km/h) with 0% gradient; stage 5, 2.5 mph with 2.5% gradient; stage 6, 2.5 mph with 5% gradient; stage 7, 2.5 mph with 7.5% gradient; stage 8, 2.5 mph with 10% gradient; stage 9, 2.5 mph with 12.5% gradient. Each stage lasted 6 minutes.

Patients were encouraged to exercise until they felt unable to continue. The exercise test was stopped at the patient's request and the reason for stopping was recorded. The ten controls followed both the heart failure protocol and the Bruce protocol to determine their maximum oxygen consumption.

MEASUREMENT OF RESPIRATORY GAS EXCHANGE
Oxygen consumption and carbon dioxide production and minute ventilation were determined by the method of Davies *et al*¹⁶ and as described below. Each subject wore a head support and J respiratory valve (Collins) and nose clip. Expired air was sampled from different ports on a seven litre mixing box (Airspec). 100% argon was added to the inlet port of the mixing box at a known flow rate. We used a mass spectrometer (Centronic Q806) to analyse mixed expired oxygen, nitrogen, carbon dioxide, and argon from the mixing box. The output of the spectrometer was known to be linear ($<1\%$ deviation) over the range of gas concentrations measured. The four channel output from the spectrometer was linked to a BBC B computer via the analogue to digital converter within the computer. Minute ventilation (VE) at body temperature, pressure, and saturation (BTPS) was calculated as follows:

$$VE = M_{\text{argon}} \times (100 - F_{\text{box Ar}}) \times 0.863 \div (F_{\text{box Ar}} - F_1 \text{ Ar}) \times (\text{barometric pressure (mm Hg)} - 47) \text{ l min}^{-1} \text{ BTPS}$$

$$M_{\text{argon}} = \text{argon flow (ml min}^{-1}) \times \text{barometric pressure (mm Hg)} \times 273 \div 760 \times (273 + \text{room temperature } (^{\circ}\text{C}))$$

where M_{argon} is argon flow in millilitres (at standard temperature and pressure, dry (STPD)) per minute; $F_{\text{box Ar}}$ is percentage concentration of argon in mixing box; and $F_1 \text{ Ar}$ is percentage concentration inspired argon (0.93%).

Oxygen consumption ($\dot{V}O_2$) in millilitres per minute (STPD) was calculated as follows:

$$\dot{V}O_2 = \frac{M_{\text{argon}} (100 - F_1 \text{ Ar})}{100 (F_{\text{box Ar}} - F_1 \text{ Ar})} \times \left[\left(\frac{F_{\text{box } N_2} \times F_1 O_2}{F_1 N_2} \right) - F_{\text{box } O_2} \right]$$

where $F_1 O_2$ is percentage inspired oxygen (20.93%); $F_{\text{box } O_2}$ is percentage of oxygen in mixing box; $F_{\text{box } N_2}$ is percentage of nitrogen in mixing box; $F_1 N_2$ is percentage of inspired nitrogen (78.09%).

Carbon dioxide production ($\dot{V}CO_2$) in millilitres per minute (STPD) was calculated as follows:

$$\dot{V}CO_2 = \frac{M_{\text{argon}} (100 - F_1 \text{ Ar})}{100 (F_{\text{box Ar}} - F_1 \text{ Ar})} \times F_{\text{box } CO_2}$$

where $F_{\text{box } CO_2}$ = percentage carbon dioxide in mixing box.

Respiratory quotient (RQ) was calculated as $\dot{V}CO_2 \div \dot{V}O_2$.

Results for $\dot{V}O_2$ and anaerobic threshold were expressed per kg bodyweight unless stated otherwise.

The computer sampled mixed expired gas every

second and averaged the results for 30 seconds. Graphs of $\dot{V}O_2$ against time, $\dot{V}O_2$ against $\dot{V}CO_2$, $\dot{V}O_2$ against ventilation rate, and $\dot{V}O_2$ against heart rate were plotted at the end of an experiment.

To validate the measurements of $\dot{V}E$, $\dot{V}O_2$, and $\dot{V}CO_2$, expired gas was collected from the exit port of the mixing box into a Douglas bag. The volume of gas collected was measured by a Parkinson-Cowan gas meter and the concentrations of mixed expired gas were analysed with the spectrometer. The calibration of the gas meter was checked with a BOC flow meter. The response time of the equipment was assessed by pumping air into the mixing box with a Rudolph syringe. Sudden changes in "ventilation" (0 to 15 litres, 15 to 20 litres, 20–30 litres, 30–40 litres, 40–50 litres, 50–60 litres) were made and the time taken to reach $\geq 95\%$ of the final minute ventilation was recorded.

MEASUREMENT OF ANAEROBIC THRESHOLD

The point at which carbon dioxide production increased disproportionately in relation to oxygen consumption was determined by two methods. It was determined subjectively by three independent observers from a graph plotting $\dot{V}O_2$ against $\dot{V}CO_2$. A satisfactory statistical technique to determine this point is not available. The following method was chosen. Maximum oxygen consumption was measured. The respiratory quotients for individual points up to 50% maximum $\dot{V}O_2$ (55% if maximum $\dot{V}O_2 < 1$ litre) were averaged and two standard deviations were calculated. Subsequent points were looked at in groups of three, that is over a period of 1.5 minutes. If two out of three respiratory quotients fell outside two standard deviations of the mean RQ then the first of the two points was taken and the $\dot{V}O_2$ at the time was recorded as the anaerobic threshold. Variation in results between observers and methods was analysed.

STATISTICAL ANALYSIS

Results are quoted as mean and standard error. Interclass differences were assessed by one way analysis of variance and Student's *t* test. The reproducibility of measures of oxygen consumption and anaerobic threshold was determined by means of the retest reliability coefficient (Rtt):

$$\left(\frac{\text{total variance reading 1} - \text{error variance}}{\text{total variance reading 1}} \right) \times 100\%$$

where error variance equals $(\text{reading 1} - \text{reading 2})^2 / \text{number of patients}$.

Results

Validation of the technique

Gas concentrations in three different samples of

each gas were measured by spectrometer. The difference between actual concentration and the measured value was $\leq 1\%$.

Douglas bag collections. The argon dilution technique underestimated $\dot{V}E$ and subsequent $\dot{V}CO_2$ and $\dot{V}O_2$, when compared with Douglas bag measurements for minute ventilation of approximately 10, 20, and 60 litres, by 2%, 3%, and 2% respectively.

Response time to changes in minute ventilation. After sudden changes in ventilation the time taken to reach 95% of the final value was ≤ 1 min.

New York Heart Association (NYHA) and specific activity scale criteria of assessment. Ten patients were NYHA class II, 14 NYHA class III (four NYHA class IIIA, 10 NYHA class IIIB). As judged by the specific activity scale assessment four were class I, six class II, 12 class III, 2 class IV.

Drug therapy

All patients were taking diuretics—mean dose of frusemide was 60 mg for patients in NYHA class II and 110 mg for those in class III. Vasodilator treatment included captopril (one patient NYHA class II, nine patients NYHA class III), nitrates (one patient NYHA class II, two patients NYHA class III); and nine patients were taking digoxin, seven of them were in sinus rhythm.

Reproducibility of oxygen consumption measurements

All patients underwent at least three exercise tests. After an initial test to familiarise patients with the treadmill maximum oxygen consumption was measured during the second and third exercise tests. The results of these two tests were compared. There was no relation between the error variance and the maximum oxygen consumption on the second exercise test ($r=0.08$). Therefore the group was analysed as a whole.

The retest reliability coefficient for maximum oxygen consumption was 90.5% for heart failure patients and 89.9% for controls. The mean maximum oxygen consumption during the third exercise test was 1% greater than that during the second exercise test (not significant).

In 10 patients (three New York Heart Association class II, three class IIIA, four class IIIB) a fourth exercise test was performed. In eight patients maximum oxygen consumption assessed in the fourth exercise test did not differ by more than 10% compared with the third exercise test but in two patients it was greater by 16% and 38%. This difference was associated with increases in exercise duration of 60% and 42% respectively.

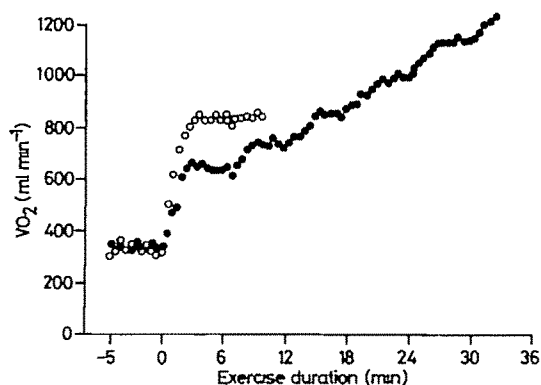


Fig. 1 Oxygen consumption ($\dot{V}O_2$) in relation to duration of exercise in one patient. The graph shows a stepped increase in oxygen consumption during treadmill exercise (●) and a sharp increase in $\dot{V}O_2$ from resting state to stage 3 of treadmill protocol (○). A steady state for oxygen consumption was reached in three minutes.

Reproducibility of anaerobic threshold measurements

In five patients the anaerobic threshold could not be assessed because of the scatter of respiratory quotient measurements. There was good correlation among three observers when the anaerobic threshold was assessed by direct inspection ($r=0.99$, 0.98). There was a strong correlation ($r=0.97$) between the results of direct inspection and those of objective assessment. The retest reliability coefficient for anaerobic threshold measurement for the second and third exercise tests was assessed for direct inspection and objective analyses of the measurement. The Rtt for assessment by direct inspection was 96% and for objective assessment it was 91%. In the two patients where maximum oxygen consumption differed by 16% and 38% for the third and fourth exercise tests the anaerobic threshold measurements differed by only -9% and 6% respectively.

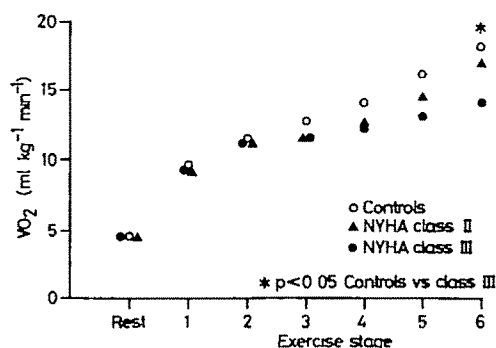


Fig. 2 Relation between oxygen consumption ($\dot{V}O_2$) and exercise stage in controls and patients in New York Heart Association classes II and III.

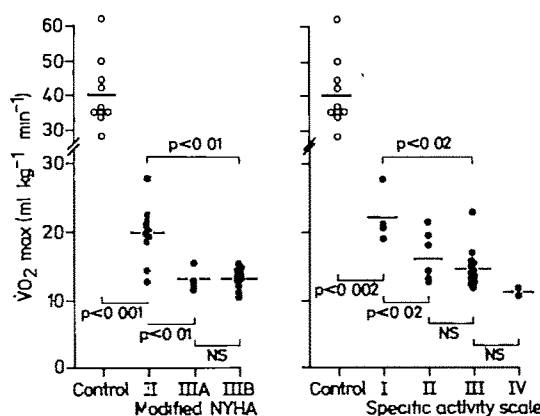


Fig. 3 Oxygen consumption in controls and cardiac patients. Relation between maximum oxygen consumption ($\dot{V}O_2$ max) and functional class according to modified New York Heart Association (NYHA) class specific activity scale. Means are indicated.

Oxygen consumption with increasing workload

No patient reached a plateau of oxygen consumption with increasing workload (oxygen consumption increase of ≤ 1 ml $\text{kg}^{-1} \text{min}^{-1}$ over previous workload)³ despite repeat exercise testing. After each change in workload, oxygen consumption reached a peak for that workload within three minutes (Fig. 1). At submaximal workloads oxygen consumption was similar in controls and in patients with heart failure, but it was lower in New York Heart Association class III patients who completed stage 6 compared with controls at the same treadmill state ($p < 0.05$) (Fig. 2).

Maximum oxygen consumption related to functional class

There was a significant difference in maximum oxygen consumption (ml $\text{kg}^{-1} \text{min}^{-1}$) between functional classes (Fig. 3). Maximum oxygen consumption results for the controls and patients in each New York Heart Association class were as follows: controls 40.1(3.1), class II 19.7(1.4), class IIIA 13.3(1.1), class IIIB 13.1(0.52). The following differences were tested for statistical significance: controls vs New York Heart Association class II ($p < 0.0001$); II vs IIIA ($p < 0.01$); and IIIA vs IIIB (not significant). Maximum oxygen consumption for each specific activity scale class were as follows: I, 22.0(1.9); II, 16.0(1.6); III, 14.4(0.83); IV 10.7(0.54). The following differences were tested for statistical significance: controls vs specific activity scale class I ($p < 0.002$); I vs II ($p < 0.02$); II vs III (not significant); and III vs IV (not significant).

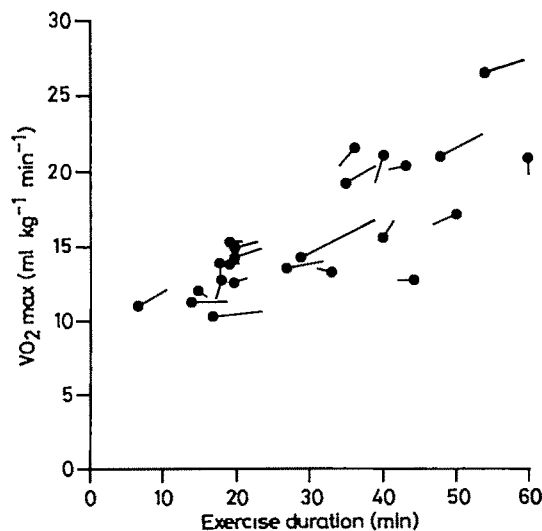


Fig. 4 Exercise duration in cardiac patients. Relation between maximum oxygen consumption ($\dot{V}O_2$ max) and exercise duration. The change in exercise duration and maximum oxygen consumption between exercise tests 2 and 3 is shown. The dot represents result of exercise test 2 and the line represents the change between test 2 and test 3

Maximum oxygen consumption related to exercise duration

Maximum oxygen consumption correlated with exercise duration though there was considerable variation in exercise duration between patients with similar maximum oxygen consumptions (Fig. 4).

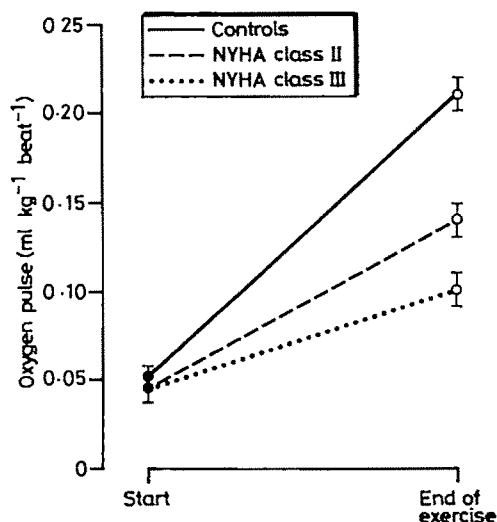


Fig. 5 Oxygen pulse at start and end of exercise and its relation to New York Heart Association (NYHA) functional class.

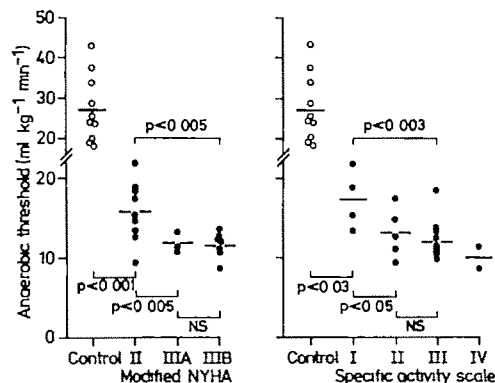


Fig. 6 Anaerobic threshold in normal subjects and cardiac patients and its relation to functional class according to modified New York Heart Association criteria and specific activity scale. Mean values are indicated

Although there was no significant difference in maximum oxygen consumption between exercise tests 2 and 3, exercise duration was longer in exercise test 3 (Fig. 4) (31 vs 26 minutes, $p < 0.05$).

Maximum oxygen consumption related to heart rate

There were significant differences in oxygen pulse (oxygen consumption divided by heart rate)¹⁷ at the end of exercise between controls and New York Heart Association class II patients ($p < 0.002$) and class II and class III patients ($p < 0.03$) (Fig. 5).

Anaerobic threshold related to functional class

Anaerobic thresholds ($\text{ml kg}^{-1} \text{min}^{-1}$) for controls and for patients in each New York Heart Association class were as follows (Fig. 6): controls, 27.5(3.0); II, 15.7(1.2); IIIA, 11.7(0.7); IIIB, 11.3(0.4). The following differences were tested for statistical significance: controls vs New York Heart Association class II ($p < 0.001$); II vs IIIA ($p < 0.007$); IIIA vs IIIB (not significant). Anaerobic thresholds for patients in each specific activity scale class were as follows: I, 17.3(1.0); II, 13.0(0.7); III, 11.8(0.5); IV, 9.5(0.5). The following differences were tested for statistical significance: controls vs specific activity scale class I ($p < 0.03$); I vs II ($p < 0.05$); II vs III (not significant).

Exercise duration related to functional class

Patients exercised for a shorter time as the degree of their functional impairment increased, though there was considerable variation (Fig. 7). The exercise duration of patients in various New York Heart Association classes was as follows: II, 39.7(3.3); IIIA, 27.6(5); IIIB, 19.1(2.9). The exercise duration of patients in specific activity scale classes were as follows: I, 44.3(3.5); II, 30.2(4.8); III, 24.9(3.2); IV,

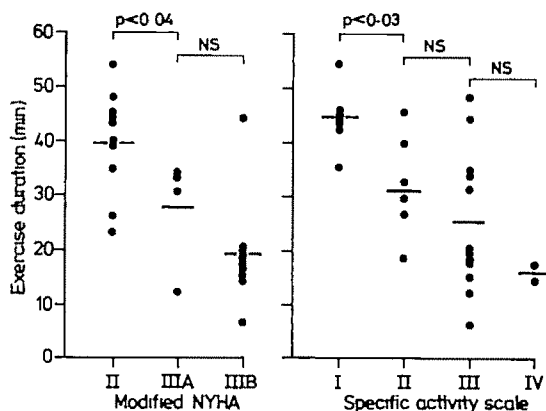


Fig. 7 Exercise duration in cardiac patients and its relation to functional class according to modified New York Heart Association criteria and specific activity scale. Mean values are indicated.

15.5(1.3). The differences between New York Heart Association classes II and IIIA ($p < 0.04$) and specific activity scale classes I and II ($p < 0.03$) were statistically significant.

Discussion

The severity of heart failure is usually graded according to the level of physical activity at which dyspnoea and fatigue appear. A more objective analysis is desirable in order to classify patients with heart failure and to assess the efficacy of treatment. Measurement of respiratory gas exchange may provide a non-invasive means of assessing functional capacity and cardiac reserve.^{3,4,6,7}

In highly motivated normal subjects oxygen consumption increases with increasing workload and then reaches a definite plateau.¹⁸ The plateau represents the physiological limit of oxygen consumption and is a measure of the total aerobic capacity of the individual. Weber *et al* noted a similar response to treadmill exercise in patients with heart failure.³ In the present study no such plateau was demonstrated despite patients being encouraged to continue the test until their symptoms became uncomfortable (Fig. 1). Maximum oxygen consumption was therefore symptom limited in these patients. There are two explanations for this difference between studies. First, the protocol used by Weber *et al*³ may have produced an artificial plateau effect because the increments in workload at the end of the protocol were smaller than those at the beginning. Second, oxygen distribution in the body may not have equilibrated in the final stage of exercise. In the present study it took three minutes before oxygen con-

sumption reached a steady state after a change in workload (Fig. 1). Consequently if the exercise test continued for less than three minutes at the final workload oxygen consumption would appear to have reached a plateau. Oxygen consumption probably failed to reach a plateau in our patients because they stopped exercising when symptoms began rather than when oxygen consumption reached its limit.

Maximum oxygen consumption was related to functional class as assessed by the New York Heart Association and specific activity scale criteria and there were statistically significant differences between some classes (Fig. 3). In other studies there was no significant difference in oxygen consumption between New York Heart Association classes II and III.^{3,8} The definition of New York Heart Association class II that we used was not the same as the original definition¹⁴ that was used by Weber *et al*³ and Franciosa⁸ and this probably accounts for the differences between studies.

In most individuals there was little change in maximum oxygen consumption when exercise testing was repeated over several days. Although maximum oxygen consumption in tests 2 and 3 was not significantly different, exercise duration and hence measured workload was significantly greater in test 3 because patients had become accustomed to walking on the treadmill. This result demonstrates that a change in treadmill performance is not a reliable indicator of a change in cardiorespiratory reserve.

Oxygen consumption generally was similar in controls and in patients with heart failure, but it was lower in New York Heart Association class III patients who completed stage 6 than in controls at the same treadmill stage (Fig. 2). This finding is consistent with other studies.^{2,19} Cowley *et al*, however, reported large differences in oxygen consumption between controls (50% higher) and patients with heart failure who exercised at a workload comparable to stage I of our protocol.²⁰ The difference occurred at the first stage of exercise and remained almost constant despite increasing exercise loads. A possible explanation is that their controls had not practiced on the treadmill and that anxiety and poor treadmill walking technique affected measured oxygen consumption. These factors may also explain the scatter of results for exercise duration and oxygen consumption noted in our study (Fig. 4).

If measurement of maximum oxygen consumption is to be useful in the assessment of patients with heart failure it must reflect cardiac status. Bias due to motivation of the patient is inherent in the measurement of maximum oxygen consumption. Measurement of anaerobic threshold may be a more objective method of assessing functional capacity.

Respiratory gas exchange analysis has been used to identify the aerobic/anaerobic threshold in patients with heart failure.^{21,22} The threshold is reached when there is a disproportionate rise in carbon dioxide production relative to oxygen consumption. This point occurs at approximately 60% of maximum oxygen consumption¹⁰ and before exercise is ended by the patient. The physiological importance of the anaerobic threshold is uncertain but the threshold is associated with a rise in plasma lactate²³ and will occur when the rate of lactate production exceeds the rate of its metabolism. Plasma lactate increases during anaerobic metabolism as a consequence of an inadequate oxygen supply to active tissue²⁴ and lactate is metabolised mainly in the liver. In heart failure lactate metabolism may be reduced because of impaired hepatic blood flow and hepatic congestion. In rats training increased the anaerobic threshold not by reducing lactate production but by increasing lactate clearance.²⁵ Thus, the lower anaerobic threshold observed in patients with severe heart failure may reflect both diminished blood flow to exercising muscle and reduced lactate clearance.

In the present study the anaerobic threshold could easily be determined by respiratory gas measurement in most patients, but in 21% of patients the scatter of respiratory quotient measurements prevented assessment by this method. Irregular breathing patterns resulted in transient fluctuations in expired carbon dioxide levels. This effect was seen in most patients at the start of exercise but persisted in some patients throughout the test. To minimise this artefact respiratory gas measurements made during the first minute of exercise were excluded from the assessment of the anaerobic threshold. In individual patients, repeated exercise testing reduced the scatter in the respiratory quotients measurements suggesting that anxiety was partly responsible. The effect was most pronounced in patients with the poorest exercise tolerance.

As expected the anaerobic threshold was lowest in the patients with more severe heart failure, though there was considerable overlap between functional classes (Fig. 6) as was also reported by Matsumura *et al.*²²

Any change in functional class in an individual patient would be expected to be accompanied by a change in anaerobic threshold. When maximum oxygen consumption alters without a change in the anaerobic threshold a change in cardiac status is questionable. In two patients maximum oxygen consumption increased by 16% and 39% in successive exercise tests yet the anaerobic threshold changed by -6% and +9% respectively and this suggests that a change in functional class had not occurred, but rather that patient motivation had altered between

the two tests.

In conclusion, maximum oxygen consumption and anaerobic threshold can be reliably measured in patients with impaired ventricular function. In most patients measurement of maximum oxygen consumption is reproducible but since it is partly determined by patient motivation it may change in the absence of a change in cardiac function. Measurement of maximum oxygen consumption alone can be misleading, but together with knowledge of the anaerobic threshold and exercise duration it provides an objective and accurate means of classifying and following patients with heart failure.

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Case reports

Hypertrophic cardiomyopathy simulating an infiltrative myocardial disease

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SUMMARY Congestive heart failure developed in a patient with low electrocardiographic QRS voltages, diffuse thickening of the septum and free cardiac wall, and a reduction in left ventricular internal diameter, which suggested an infiltrative heart muscle disease. Histological examination at necropsy showed hypertrophic cardiomyopathy with symmetrical left ventricular hypertrophy. Myocardial disarray of type 1A disorganisation was extensive and equally distributed in the ventricular septum and the left anterior and left posterior ventricular free walls. Severe fibrosis (40%) was also present and may have been a possible cause of the electrocardiographic abnormalities as well as of the lack of ventricular dilatation.

Hypertrophic cardiomyopathy, particularly at an advanced stage, manifests physical signs^{1,2} and electrocardiographic³ and echocardiographic⁴ changes, which aid in the clinical diagnosis. Congestive heart failure may complicate advanced hypertrophic cardiomyopathy and make the diagnosis more difficult.

We report a patient with congestive heart failure in whom electrocardiographic and echocardiographic changes suggested an infiltrative heart muscle disease and histological examination at necropsy showed typical features of hypertrophic cardiomyopathy with symmetrical left ventricular hypertrophy.

Case report

A 70 year old man was admitted because of congestive heart failure. For the previous two months he had complained of fatigue and dyspnoea, which were progressive and accompanied by oedema in the lower limbs and ascites. His clinical and family histories were unremarkable: in particular he denied any previous history of systemic hypertension or heart murmurs or instance of sudden death in first degree relatives.

Previous chest radiographs and electrocardiograms were unavailable. On physical examination he was in great distress with anasarca and jugular venous con-

gestion. His heart rate was regular at 110 beats/min. The heart sounds were muffled and a gallop rhythm was present. No cardiac murmurs were heard. Blood pressure was 100/80 mm Hg. Chest radiographs showed mild cardiomegaly, pulmonary congestion, and a bilateral pleural effusion. Renal function tests and examination of the ocular fundus were normal, and possible cardiac damage secondary to chronic high blood pressure was excluded.

An electrocardiogram (Fig. 1a) showed low QRS voltages, first degree atrioventricular block (PR interval 0.26 ms), and poor progression of the R wave in the right precordial leads. Cross sectional echocardiography (Fig. 1b) showed diffuse severe thickening of the interventricular septum as well as of the left and right ventricular free walls. The left ventricular end diastolic dimension was reduced (37 mm); the right ventricular maximum dimension assessed in the four chamber apical projection was 27 mm. Mild left ventricular hypokinesia was present. Left and right atrial sizes were within normal limits. The inferior vena cava and hepatic veins were dilated. An M mode echocardiogram showed anterior motion of the mitral valve leaflet and a reduced E-F slope; systolic motion was normal. Tricuspid, aortic, and pulmonary valve movement was normal. The thickness of the interventricular septum and the posterior wall was 23 mm at the level of the mitral valve tip and papillary muscles.

Because of the congestive heart failure, treatment with digoxin 0.125 mg/day, diuretics (frusemide 25

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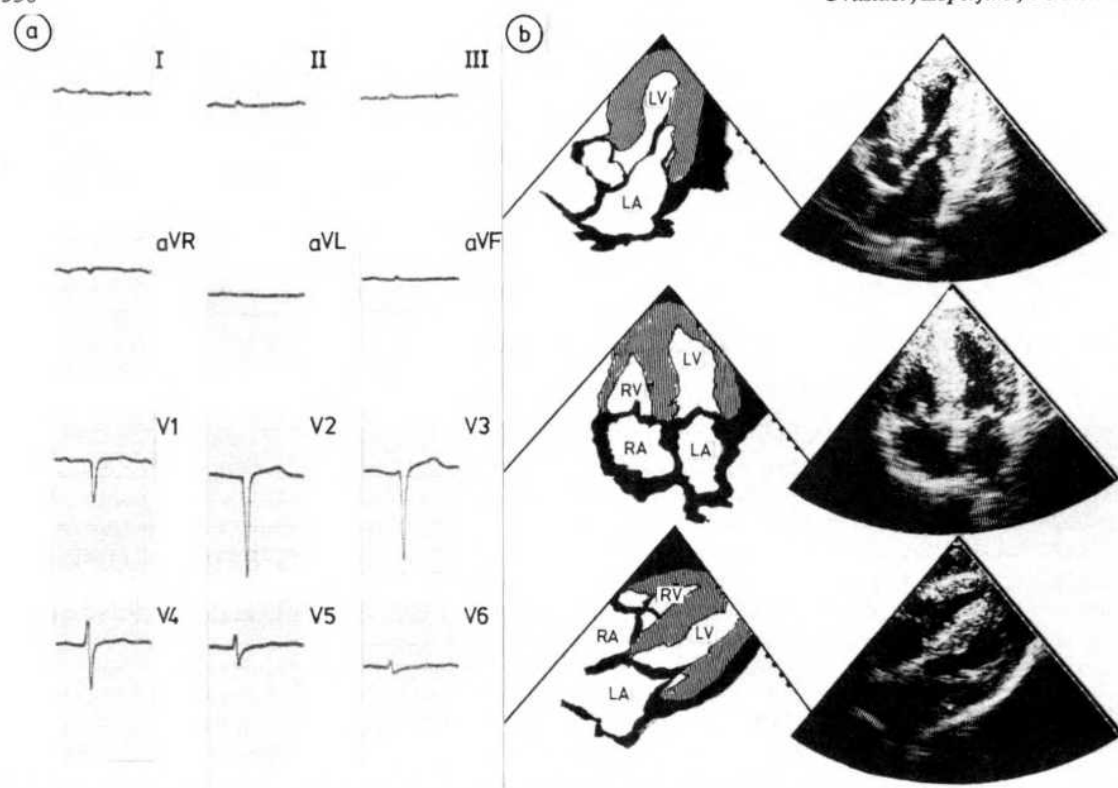


Fig. 1 (a) Cross sectional echocardiograms in the two chamber apical view (top), the four chamber apical view (middle), and the four chamber subxiphoid view (bottom) showing diffuse thickening of the septum and ventricular free walls and a small left ventricular cavity. (b) Standard electrocardiogram showing first degree atrioventricular block, low QRS voltages in the peripheral leads, and poor progression of R wave in the right precordial leads.

mg/day and spironolactone 100 mg/day), and salt free albumin 25 g/day was started. Seven days later the patient's clinical condition improved. The ascites and peripheral oedema disappeared and the pleural effusion was no longer visible on radiographs. The electrocardiographic abnormalities were unchanged and the heart rate was reduced to 85 beats/min. A ventricular endomyocardial biopsy was not undertaken as the patient suffered a stroke and died on the tenth day of admission.

NECROPSY FINDINGS

On macroscopic examination the heart was hypertrophied and firm to the touch. The hypertrophy was concentric, the septum and posterior and lateral free walls each measuring 23 mm at mid-ventricular level. The left ventricular cavity was reduced in size, but the right one was normal. The atrioventricular valves were thickened along the free margin. The endocardium showed no abnormality. Apart from minor arteriosclerotic thickening, the coronary arteries were normal. No necrotic or fibrotic areas were seen.

Histological examination

Method—Tissue sections were taken from the septum and the anterior and posterior left ventricular free walls about halfway between the aortic valve and left ventricular apex. In the anteroposterior plane the tissue sections were obtained from the full thickness of the ventricular septum, the anterior left ventricular free wall about 2 cm from the left anterior descending coronary artery, and the posterior left ventricular free wall between the papillary muscles. All tissue specimens were fixed in 10% formalin and embedded in paraffin. Five micrometre thick sections were cut on a base sledge microtome and stained with haematoxylin and eosin, Miller's elastic van Gieson stain,⁵ and congo red (for amyloid). The diameter of the myocardial fibres in the area of the nucleus was measured at a magnification of $\times 460$. The interstitium was measured using a grid and point counting system.⁶ Cardiac muscle cell disorganisation was quantified using Maron's grading system.⁷

Findings—In the middle layer of the myocardial wall, the septum, and the left anterior and posterior

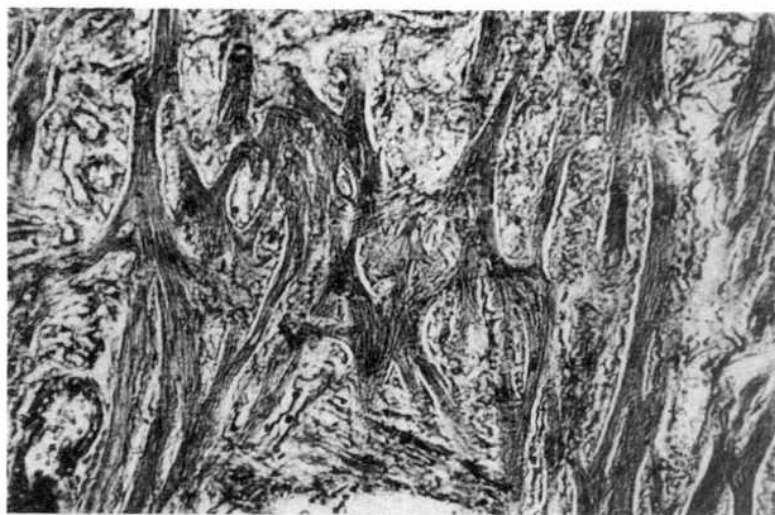


Fig. 2 Photomicrograph showing severe hypertrophy with type 1A disorganisation of myocardial fibres and extensive fibrosis interrupting the cardiocytes. (Haematoxylin and eosin $\times 100$.)

ventricular free walls the myocardial fibres were severely hypertrophied (measuring $60\text{ }\mu\text{m}$ in diameter) and in total disarray. In particular, adjacent cardiac muscle cells cut longitudinally were aligned perpendicularly or obliquely to each other (Fig. 2) in accordance with the type 1A disorganisation of Maron's classification.⁷ Quantitative analysis of the distribution of myocardial cell malalignment in the three regions of the left ventricle showed that the mean area of disorganised muscle cells per section was 45% in the left ventricular septum, 44% in the left anterior ventricular free wall, and 44.5% in the left posterior ventricular free wall. The nuclei were bizarre in shape, and several were surrounded by a clear zone, the so called perinuclear halo. The interstitium was severely widened, occupying more than 40% of the areas assessed morphometrically; the interstitium projected between the myocardial fibres and interrupted the cardiocytes (Fig. 2). The special staining for amyloid showed a negative result. The histological hypertrophic cardiomyopathy index was 80%, which is well within the limit of diagnostic reliability for hypertrophic cardiomyopathy.⁸

Discussion

The histological features in our patient were typical of hypertrophic cardiomyopathy. The diagnosis was supported by the presence of severe hypertrophy with disarray of myocardial fibres, bizarre shaped nuclei, extensive fibrosis, and a perinuclear halo, which together produced a diagnostic hypertrophic cardiomyopathy index of 80%.⁸ Because of the diffuse

thickening of the left ventricular wall (septal to posterior wall thickness ratio 1.0), this patient had a symmetrical form of hypertrophic cardiomyopathy. Shapiro and McKenna reported the clinical findings in patients with hypertrophic cardiomyopathy and symmetrical left ventricular hypertrophy.⁹ To our knowledge, however, the necropsy findings in such patients have not yet been reported.

In our case, a qualitative analysis of cardiac muscle cell alignment showed a type 1A disorganisation according to Maron *et al*'s classification.⁷ The extent of myocardial cell malalignment, studied quantitatively by Maron's grading system, was great (mean area of disorganised cells per section 44.5%) and equally distributed in the septum and the left anterior and left posterior ventricular free walls.

Further features of our patient were the unusual clinical presentation and the echocardiographic findings. Cross sectional echocardiography showed severe thickening of the interventricular septum and the left and right ventricular free walls. The left ventricular cavity was considerably reduced in size and left ventricular contractility was slightly decreased. In the absence of systemic hypertension or aortic valve disease these findings are consistent with an infiltrative heart muscle disease or hypertrophic cardiomyopathy. The electrocardiographic changes of low QRS voltages were, however, more suggestive of the first process.¹⁰ Nevertheless, the clinical as well as the necropsy findings failed to show any common cause for these electrocardiographic abnormalities. In particular, the heart was normally sited in the chest, and a pericardial effusion as well as pulmonary

emphysema were absent. A possible explanation for the low voltages in this case of hypertrophic cardiomyopathy may have been the extensive fibrosis which occupied more than 40% of the areas assessed morphometrically. Some authors have reported patients with hypertrophic cardiomyopathy in whom the QRS voltages had fallen over approximately 10 years.³ We suggest that fibrosis in hypertrophic cardiomyopathy is a progressive time-dependent phenomenon that produces electrical loss if life threatening ventricular arrhythmias do not interrupt its natural course.

Cardiac failure in patients with hypertrophic cardiomyopathy is rarely associated with left ventricular dilatation¹¹⁻¹³ and mostly affects patients who have undergone myotomy-myectomy.¹³ In our patient the extensive fibrosis could have prevented the development of cardiac dilatation. Quantitative studies of a large number of patients with hypertrophic cardiomyopathy and congestive heart failure would be required to test this hypothesis.

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Management of aortic left ventricular tunnel

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SUMMARY A 22 year old man had a diagnosis of left ventricular aortic tunnel established during infancy. Surgical repair was deferred at that time because his severe aortic root deformity would also have required aortic valve replacement. His current lack of symptoms together with a normal exercise capacity could be used as an argument against routine early surgical repair of the tunnel, particularly when the possible need for additional aortic valve replacement is considered.

Aortic left ventricular tunnel is a rare congenital cardiac malformation. The physiology of this cardiac defect is similar to that of aortic valvar regurgitation. Surgical repair of the tunnel, even in the absence of heart failure, is the usual management.¹⁻³ Gross aortic valve deformity is, however, usually already present in the neonatal period, most probably as a result of the turbulence through the tunnel in utero. Despite successful surgical closure of these tunnels most patients are left with haemodynamically important aortic regurgitation and will need aortic valve replacement in the future.

We report a patient with severe left ventricular volume overload who was without symptoms. Structural change in architecture of the left ventricular muscle may have developed in utero in response to the early expansion of left ventricular volume. The continued stability of the patient's cardiac function and lack of symptoms are an argument against early surgical repair.

Case report

NEONATAL HISTORY

A 22 year old man was referred to our hospital at 6 weeks' old because of a cardiac murmur. Labour and delivery had been normal at 36 weeks' gestation (birthweight 2.85 kg). He was a healthy looking baby, without cyanosis or signs of heart failure. All peripheral pulses were present and collapsing in character. A pronounced apical and left parasternal heave was present. Auscultation detected a grade 3/4 ejection systolic murmur and a 3/4 decrescendo

diastolic murmur over the entire precordium.

A radiograph of the chest showed pronounced cardiomegaly with a grossly dilated aortic root and ascending aorta. The lung fields were normal. A clinical diagnosis of aortic regurgitation was made, and this was subsequently changed to aortic left ventricular tunnel when this was first described shortly afterwards.⁴ He was without symptoms, and subsequent growth and development were normal. The clinical diagnosis was confirmed by cardiac catheterisation at the age of 4 years. Measurements of right heart pressures were normal. Ascending aortic diastolic pressure was 40 mm Hg, and left ventricular end diastolic pressure 13 mm Hg. Right heart oximetry excluded a left to right shunt. Aortography showed gross dilatation of the aortic root, with pronounced expansion of the right and non-coronary sinuses. The tunnel was evident and arose at the level of the right coronary sinus. Immediate opacification of the left ventricle through both the tunnel and the aortic valve occurred. The aortic cusps seemed to be grossly deformed. Since surgical repair would probably have also entailed aortic valve replacement and especially as the patient was symptomless operation was deferred. Throughout childhood he remained completely symptomless and as an adult led a normal active life. At school he played competitive sport including soccer, without developing symptoms. At yearly review the results of his physical examinations were unchanged. Blood pressure remained at about 140/20 mm Hg and systolic ejection and early diastolic murmurs were repeatedly heard all over the precordium. Electrocardiograms always showed voltage criteria of left ventricular hypertrophy and no ST-T abnormality. By chest radiography the cardiothoracic ratio was unchanged

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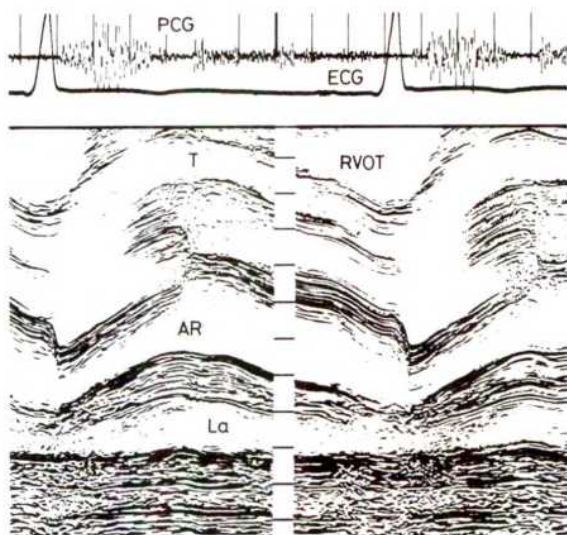


Fig. 1 M mode echocardiogram showing the left ventricular aortic tunnel (T) in between the aortic root (AR) and the right ventricular outflow tract (RVOT). La, left atrium; PCG, phonocardiogram; ECG, electrocardiogram.

(59%), and was proportionately identical with that on the radiographs during infancy.

Serial M mode echocardiograms were repeated after the age of 6 years. The left ventricle was hypertrophied symmetrically, its volume had increased, and fractional shortening was 45–55% when corrected for body surface area. The anterior leaflet of the mitral valve had always shown a decreased excursion and fluttering throughout diastole. In all the serial studies a chamber was seen lying between the anterior wall of the aortic root and the right ventricular outflow tract (Fig. 1), below and at the level of the aortic annulus. This space had become continuous with the aortic root above the annulus.

Cross sectional echocardiography clearly showed the tunnel, which was best visualised in the parasternal long axis view (Figs. 2(a) and 2(b)). The tunnel entered the left ventricle at the upper part of the septum beneath the aortic root and was continuous with the right aortic sinus of Valsalva. The leaflets were considerably thickened and deformed. Symmetrical hypertrophy and increased left ventricular volume was seen by M mode echocardiography. From the aortic short axis (Figs 2(c) and 2(d)) three valve cusps could be seen; they were all severely

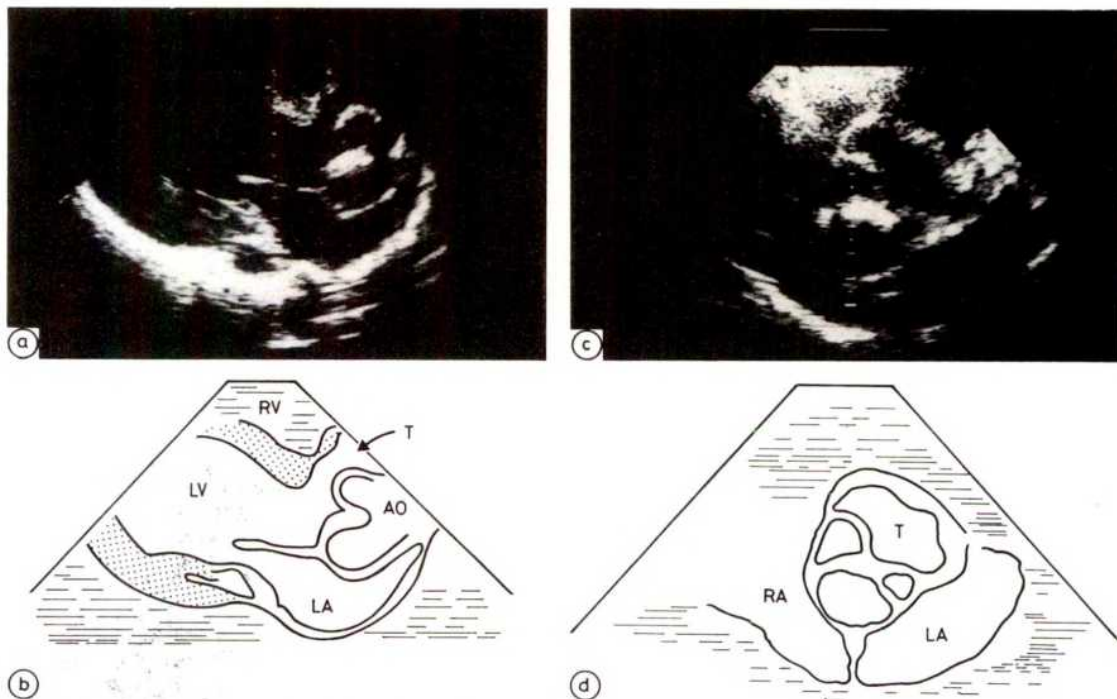


Fig. 2 (a) parasternal long axis recording of the left ventricle (LV) and (b) parasternal short axis recording of the aortic root with accompanying diagrams showing the appearance of the left ventricular aortic tunnel (T). Note the thickened tricuspid aortic valve (b). RV, right ventricle; AO, aortic root; LA, left atrium; RA, right atrium.

thickened and deformed. A rudimentary left coronary cusp and a large ballooning right coronary cusp were seen. Scans from the aortic root showed the tunnel extending from the aortic root at the level of the right coronary sinus of Valsalva to the left ventricle. The tricuspid and pulmonary valves looked normal, and the left atrium and right sided heart chambers were of normal size.

Discussion

Since Levy *et al* first described aortic left ventricular tunnel in 1963⁴ 33 cases have been reported. The aortic left ventricular tunnel is a vascular channel of congenital origin that connects the aortic root in the region of the right coronary sinus of Valsalva (above the aortic valve) with the left ventricle immediately below the aortic valve annulus. The aortic valve is often deformed,^{1,3-6} and other cardiac abnormalities may be associated.^{4,7-11} These findings and the subsequent hypertrophy of the left ventricle have been found at operation or necropsy^{12,13} from the neonatal period onwards.¹¹

Although there is evidence to support the congenital nature of left ventricular aortic tunnel, the embryology of the tunnel is controversial. Cooley *et al* postulated Marfan's syndrome based on the aneurysmal dilatation of the sinus of Valsalva with an excess deposition of mucopolysaccharide substances in the elastic media of the aortic wall and the adjacent portion of the tunnel.⁶ It was proposed that this could lead to cystic areas, which in turn could rupture into the left ventricle. These views, however, have not found support. Levy *et al* showed continuation of the elastic fibres of the aortic media into the tunnel wall and suggested that the tunnel was an anomalous coronary artery that communicated through an enlarged myocardial sinusoid with the left ventricle (coronary-cameral fistula).⁴ The tunnel wall in the ventricular septum represented histologically a sinusoid consisting mainly of connective tissue. Roberts and Morrow, however, concluded that the structure of the tunnel differed from that of the blood vessel.⁶

The diagnosis should be suspected in neonates presenting with signs of aortic regurgitation. The differential diagnosis is between absent aortic valve, endocarditis with destruction of the aortic valve, and tetralogy of Fallot with absent pulmonary valve.⁷ Rarely an aneurysm of the sinus of Valsalva may dissect into the left ventricle through the ventricular septum.¹⁴

Echocardiography is complementary to invasive studies, especially in detecting other associated cardiac abnormalities such as aortic and pulmonary stenosis³ or, less commonly, compression of the left

coronary artery by a deformed aortic valve.⁹ Cross sectional echocardiograms should detect progressive compression of the right ventricular outflow tract by the tunnel.¹⁰

Various method of surgical repair have been reported—for example, direct closure and external plication. Aortic regurgitation often persists post-operatively. Spooner *et al* reported a "triple repair" that was used successfully in one case.¹⁵ At the time of publication aortic regurgitation was not present. Similarly, in three cases where patch closure was used aortic regurgitation was avoided.^{7,10,16}

The risk of surgical repair was 10%, and even if the surgical repair is performed in the neonatal period or early infancy aortic valve deformities are already present.^{3,11,15,17,18} These and aortic root abnormalities can be explained by turbulent flow through the tunnel, beginning in utero.

The natural history of the left ventricular aortic tunnel is not known, and the oldest patient reported was a 25 year old man who was symptomless until he died of bacterial endocarditis.¹³

Three patients who had surgical repair and were symptomless were left with aortic regurgitation.¹⁻³ Two other patients with symptoms died without surgical intervention, but they had other major cardiac defects.^{6,19} In our patient the need for aortic valve replacement at an early age because of gross aortic valve deformity was the main reason for deferring surgery during childhood.

A valve defect occurring in utero may be better tolerated than a similar one occurring after birth. The earliest recognisable embryonic cardiac system is a straight heart tube. The visible contraction of this tube is similar to peristaltic movements propelling blood unidirectionally.²⁰ Growth of this primitive heart results in the formation of a cardiac loop and later the cardiac septa. Throughout this development the basic direction of the peristaltic wave is well preserved, and there are recognisable features of this in the adult heart.²¹ The formation of the cardiac valves is not complete until the ninth week, by which time the four chambers of the heart are fairly well formed. The primitive fetal heart is therefore adapted to pumping without the help of heart valves. Persistent incompetence of the valves beyond the ninth week would tend to exert development pressure on the fetal heart to adapt and to retain some of the peristaltic form of contraction and hence to preserve pumping efficacy into adulthood. This might lead to modification of the myocardial fibre direction and of the activation and deactivation sequence. At the molecular level there may be functional adaptation in the fetal contractile units, such as in terms of selection of the myosin types^{22,23} and hyperplasia of the myocardial cells.

An expectant attitude to the treatment of aortic left ventricular tunnel may be justified on account of favourable adaptation of the developing heart to this anomaly in utero. These considerations may explain the favourable prognosis of such patients compared with the less good outlook for most patients with severe aortic regurgitation acquired in childhood or adult life.

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Right atrial spleen

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SUMMARY A large cardiac tumour occupying most of the right atrium and the right ventricle and causing inflow obstruction to the right heart was confirmed by cross sectional echocardiography in a 41 year old man. After surgical resection histological examination showed that the atrial tumour had the characteristics of splenic tissue. Possible mechanisms for the development of such a tumour include an origin analogous to that of an accessory spleen or the implantation and subsequent growth of lymphoid tissue in a pre-existing superior vena caval or high right atrial angioma.

Primary cardiac tumours are rare. In necropsy series the incidence is extremely low (0.0017-0.28%). In most reported series about 75% of all cardiac tumours are considered to be benign histologically. Angiomas account for less than 5% of the total number. They are more common in the right heart chambers and generally as sessile. Histologically, the tumours consist of spaces lined with endothelium, which may contain blood, lymph, or thrombi.¹

We report a patient who presented with signs of inflow obstruction to the right heart due to an atrial tumour with an unusual histological appearance.

Case report

A 41 year old man was admitted because of slowly progressive dyspnoea and ascites. A cardiac murmur had been heard when he was 5 years old. Until 1980 he had worked as a waiter and for 20 years had consumed large amounts of alcohol. He was referred to our hospital with a presumptive diagnosis of alcoholic liver cirrhosis.

On physical examination the jugular veins were severely congested with a very prominent "a" wave. The heart was not enlarged. A grade 2/6 high frequency pansystolic murmur and a grade 2 high frequency diastolic murmur with presystolic accentuation were loudest at the left sternal border. The abdomen was distended by ascites, and the liver and spleen were not palpable. There was, however, no peripheral oedema.

A 12 lead electrocardiogram showed sinus rhythm with an undetermined mean frontal plane QRS axis.

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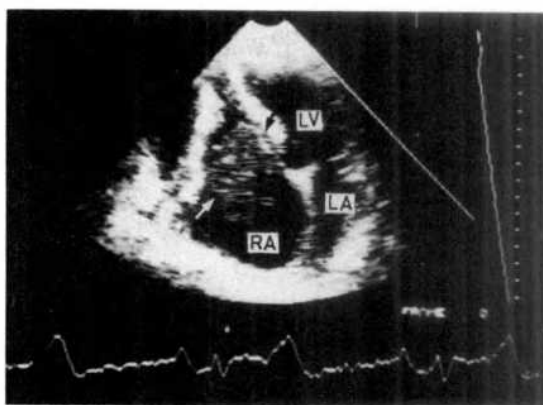


Fig. 1 Cross sectional echocardiogram in the apical view showing an echo dense mass at the level of the right atrioventricular valve annulus partially occupying the right atrium as well as the right ventricle. The arrow probably indicates an adherent part of the septal tricuspid leaflet.

In all 12 leads the QRS complexes showed low voltage, and the P waves had a normal voltage in the limb leads. There was a disproportionate relation between the amplitude of the P waves and that of the QRS complexes. Chest radiographs showed clear lung fields and a moderately enlarged heart in the posteroanterior projection.

The phonocardiogram showed a high frequency diastolic murmur with presystolic accentuation starting 0.10-0.12 s after the second heart sound. The raised central venous pressure, the pronounced "a" wave in the venous pulse tracing, signs of tricuspid disease, and the absence of signs of left heart failure, pulmonary hypertension, or pericardial disease suggested an inflow obstruction to the right heart. This

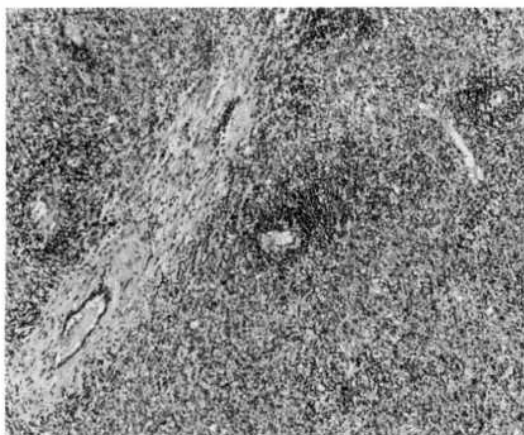


Fig. 2 Microscopical appearance of the right atrial tumour showing a thick walled artery surrounded by a mantle of lymphocytes forming a sheath around these arteries. (Giemsa stain $\times 150$.)

was confirmed by cross sectional echocardiography. An apical approach showed a non-mobile, homogeneous echo dense mass occupying most of the right atrium and extending across the tricuspid valve into the right ventricular cavity (Fig. 1). The echocardiographic diameter of the mass was $7 \times 4 \times 4$ cm. The nature of the mass could not be specifically identified. The pattern of motion of the echo on M mode echocardiography was not, however, characteristic of a myxoma.

SURGICAL FINDINGS

The chest was entered through a midline sternal incision. From the outside the right ventricle looked severely hypoplastic, with the left anterior descending coronary artery displaced rightwards. The right atrial wall was severely hypertrophied. The right atrium contained a dark and smooth solid tumour attached by a single short cord like pedicle to the lowest segment of the superior vena cava. The tumour extended across the tricuspid annulus into the right ventricle. The tricuspid valve leaflets were deformed and fenestrated. Half of the septal and anterior leaflets were adherent to the right ventricle and only the posterior leaflet retained some mobility. The papillary muscles were hypoplastic and the chordae tendineae were very short. The tumour and tricuspid valve were removed and a Ionescu-Shiley prosthetic valve (size 31) implanted in the tricuspid annulus. The patient died 15 days after the operation as a result of septic shock.

HISTOLOGICAL FINDINGS

The surgical specimen was fixed in 4% neutral phosphate buffered formaldehyde. Tissue samples were embedded in paraffin and epon for light microscopy

and electron microscopy respectively. Sections cut at $5 \mu\text{m}$ were stained with haematoxylin and eosin, Giemsa, Gordon and Sweet's reticulin, periodic acid Schiff (PAS), Alcian blue, van Gieson's elastic tissue stain, Perl's stain for iron, and methyl green pyronine.

The tumour, which measured $7 \times 5 \times 4$ cm, was enclosed within a thin greyish white capsule, which was continuous with the endothelial lining of the atrium. The cut surface varied in colour from deep red to greyish red.

Light microscopy showed that the tumour was surrounded by a collagenous capsule. The pedicle contained only collagenous connective tissue and was traversed by both arteries and veins. The parenchyma showed a reticular framework and endothelial lined sinusoids, some of which had cystic dilatations. The sinusoids were filled with red cells and had foci of haematopoiesis. Thick walled arteries were present and small lymphocytes formed a sheath around these arteries. The microscopical appearance was identical to that of normal splenic tissue except for a paucity of trabeculae (Fig. 2).

Electronmicroscopy showed an intermingling of small capillaries, red blood cells, and some lymphocytes. The capillaries consisted of a single layer of irregular endothelial like cells with cell junctions and a periendothelial basal lamina. Pericytes and histiocytes were not found. The appearance was similar to that of splenic tissue.

When the tumour was compared with splenic tissue obtained at necropsy by immunoperoxidase techniques for identifying immunoglobulins in plasma cells as well as histiocytic markers no differences could be found.

NECROPSY FINDINGS

At necropsy an enlarged spleen weighing 320 g was present at the normal site in the left upper abdomen and showed no abnormalities other than signs of septicæmia and small foci of haematopoiesis. The liver was moderately enlarged, weighing 1940 g. The parenchyma showed severe cardiac fibrosis and steatosis.

Discussion

The most striking feature of this case was the hitherto unreported finding of a cardiac tumour consisting of splenic tissue. Several possible mechanisms for the pathological development of a right atrial spleen exist. Embryologically, the primordium of the spleen appears as a thickening of coelomic epithelium on the left side of the dorsal mesogastrium. Several separate splenic masses originate here simultaneously and fuse to form a lobulated spleen.² Failure of the adjoining

splenic areas at the dorsal mesogastrium to fuse could give rise to the formation of an accessory spleen. Invagination of a splenic area during cardiac development could explain the finding of accessory intracardial splenic tissue, but this seems to be rather unlikely. Another possibility is a primary cardiac tumour of an angiomatous nature. Such tumours probably arise from angioblasts normally dormant in the myocardium. The angioblasts originate from primitive mesenchymal tissue and produce blood vessels, primitive plasma, and red blood cells.^{3,4} One theory focuses on the vasoformative reserve cell. Islands of vasoformative reserve cell hyperplasia may occur in the endocardium near the fossa ovalis. The spleen is essentially a part of the vascular system, and the vasoformative reserve cells could presumably also give rise to the development of an angiomatous tumour differentiating as splenic tissue. This angiomatous tissue might have become seeded by lymphocytes. The lymphoid tissue in the tumour is thought to be formed by a proliferation of lymphocytes in the area. Foci of haematopoiesis were present in both the tumour and the spleen. This myeloid metaplasia in the spleen is due to the undertaking of haemopoietic functions by the reticuloendothelial cells.⁵ Both the tumour and the patient's spleen cells showed this myeloid metaplasia. Furthermore, even the neoplastic nature of the tumour in our patient was unknown, since it is almost impossible to differentiate between malformations—such as hamartomas—and benign neoplasms of blood vessels on purely anatomical or clinical grounds.

From a clinical point of view the following findings are of special interest. The average delay between the onset of symptoms and the diagnosis of right atrial tumours in most reported cases was three years.¹ In our patient the history of a large consumption of alcohol and the pronounced ascites many years previously had led to an initial false diagnosis of alcoholic liver cirrhosis. A combination of features—namely, the high central venous pressure, the pronounced "a" wave in the venous pulse tracing, and the diastolic murmur with presystolic accentuation—suggested the possibility of a right sided inflow obstruction at the level of the tricuspid valve. The high frequency of the diastolic murmur is, however, unusual in tricuspid

inflow obstruction. Nevertheless, because the large solid tumour was wedged in the tricuspid orifice this characteristic of the murmur may be explained by the very high central venous pressure (25 mm Hg) and the subsequent contraction of the hypertrophied right atrium forcing the blood around the tumour via the slit like opening in the right ventricle. A definitive diagnosis was made by cross sectional echocardiography, which allowed the size of the tumour to be accurately estimated. Cross sectional echocardiography seems to be ideally suited for the non-invasive diagnosis of a right sided cardiac mass.⁶ The degenerative changes of the tricuspid valve were unusual. Fenestration of the atrioventricular valve leaflets, short chordae tendineae, and hypoplasia of the papillary muscles have not been reported in cases of atrial myxoma.

In conclusion we were unable to differentiate this cardiac atrial tumour from splenic tissue. The clinical findings suggest that the tumour had been present for a long time, which may indicate a congenital origin. Nevertheless, the true origin of this unusual tumour remains unknown.

We thank Professor A E Becker, University of Amsterdam, for his most valuable opinion on this case and Professor E O Robles de Medina for his encouragement and advice.

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Early prenatal detection of double outlet right ventricle by echocardiography

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SUMMARY A double outlet right ventricle with subpulmonary ventricular septal defect and right sided hypoplastic aorta was diagnosed in a 22 week fetus of a mother with diabetes mellitus. Elective termination of pregnancy was carried out and the echocardiographic findings were confirmed. Early prenatal detection of congenital heart disease may allow elective termination of pregnancy when the fetus has severe defects.

The first description of double outlet right ventricle was provided in 1793 by Abernethy,¹ which was subsequently given the term "double outlet right ventricle" by Witham in 1957.² Double outlet right ventricle is a rare condition forming $\leq 1\%$ of all congenital heart defects, and the term refers to a group of complex and heterogenous malformations that have in common only the origin of both great vessels from the right ventricle. Other cardiac malformations are always present, and frequently multiple abnormalities coexist. These may include one or more ventricular septal defects, systemic or pulmonary or left ventricular outflow obstruction, and major atrioventricular valve abnormalities.

Double outlet right ventricle may occur with any atrial situs, several different atrioventricular connections, and many other variations. Situs solitus and atrioventricular concordance are, however, the most common findings.

Cross sectional echocardiography has proved useful in the diagnosis of double outlet right ventricle. A segmental sequential approach that reliably identifies both ventricles and great vessels is mandatory. Many of the associated cardiac lesions are of paramount clinical importance and are recognisable by echocardiography. These features of diagnosis are critical in prenatal diagnosis as echocardiography is the only tool available, and further advice and obstetric management must be based on these findings.

We report the detection of double outlet right ventricle with subpulmonary ventricular septal defect and a right sided hypoplastic aorta in a 22 week old fetus of a mother with diabetes mellitus class C, type I (White classification).³

Case report

A 21 year old gravida 1 with diabetes mellitus type C, who had been diabetic since the age of 13 years, underwent amniocentesis at 16 weeks' gestation, which showed a normal female karyotype. She was referred to this unit for prenatal echocardiography in view of the known association of cardiac structural abnormalities in the offspring of diabetic patients. Ultrasonic examination of the fetus was carried out at 22 weeks' gestation with a Dasonics Cardio Vue 100 mechanical sector scanner with 5 MHz transducer. Fetal size was appropriate for gestational age. Scanning of the fetal heart showed atrioventricular concordance and a large subpulmonary ventricular septal defect. Both great vessels were connected to the right ventricle with a side by side position with the aorta, which appeared hypoplastic, to the right of the pulmonary artery (Fig. 1a). The pulmonary artery was seen to be continuous with the mitral valve. No other structural anomalies were observed in the fetus.

NECROPSY FINDINGS

The parents were informed of the findings and requested termination of the pregnancy, which was performed at 23 weeks' gestation. A female fetus weighing 400 g was delivered. Postmortem examination of the heart confirmed the antenatal echocardiographic findings. There was a large subpulmonary

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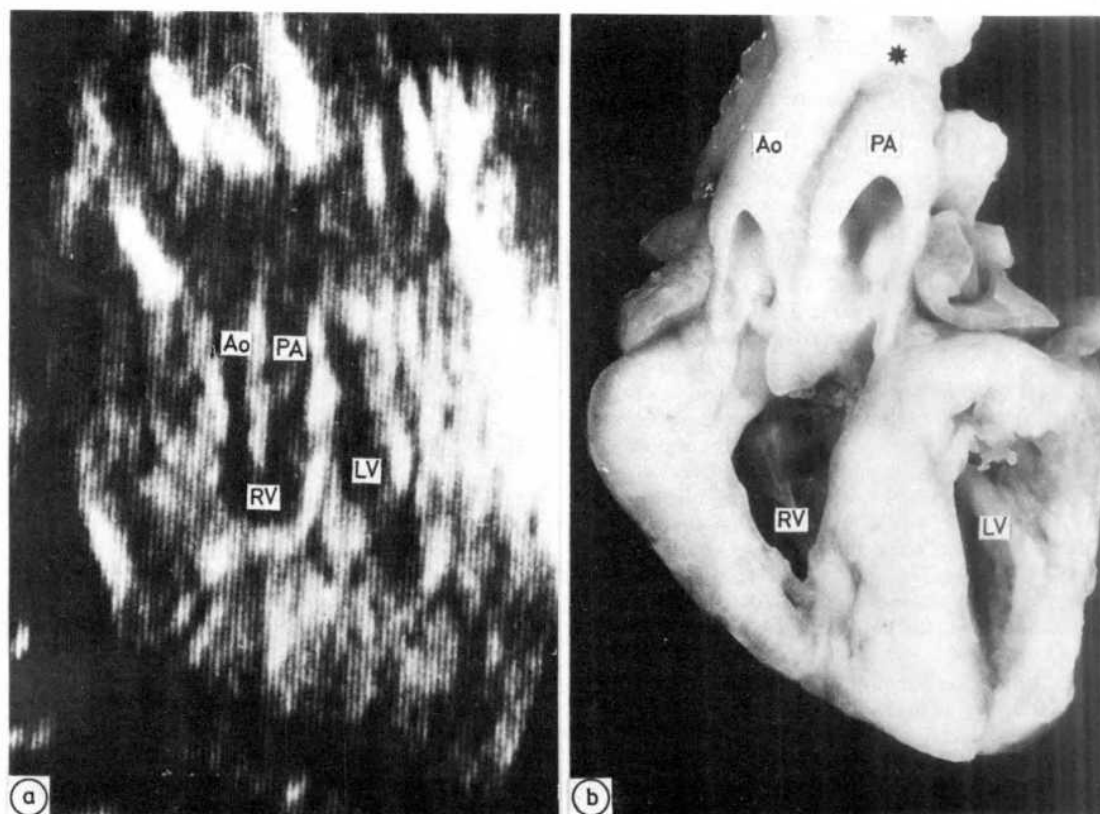


Fig. (a) Longitudinal cross sectional echocardiogram in the fetus showing both great vessels connected to the right ventricle (RV). In real time images the aorta (Ao) was traced to the head and neck vessels and looked hypoplastic; the pulmonary artery (PA) was also traced to its bifurcation. The ventricular septal defect was not visualised in this plane. (b) Morphological appearance of the fetal heart cut in a section equivalent to the echocardiogram in (a). The outflow tract into the aorta is narrow and the ascending aorta slightly underdeveloped. There is tubular hypoplasia (*) between the left subclavian and left common carotid arteries. LV, left ventricle.

perimembranous ventricular septal defect and a slit-like muscular ventricular septal defect in the inlet septum. Both great vessels were connected to the right ventricle with the aorta to the right of the pulmonary artery (Fig. 1b). There was subaortic stenosis and slight underdevelopment of the descending aorta. Tubular hypoplasia of the aortic arch was found between the left subclavian and left common carotid arteries. The pulmonary valve was in fibrous continuity with the mitral valve. No other structural anomalies were present in the fetus.

Discussion

Diabetes mellitus is known to be associated with an increased risk of fetal abnormalities,^{4,5} including skeletal, central nervous system, genitourinary, gastrointestinal, and cardiac anomalies. Cardiovascular

anomalies may occur in approximately 5% of these infants.^{6,7}

Amniocentesis, which in this unit is performed routinely in juvenile diabetics for alpha fetoprotein estimation and karyotyping, had been performed at 16 weeks' gestation and showed a normal concentration of alpha fetoprotein and normal female karyotype. Had this not been the policy karyotyping would have been performed after detection of the cardiac abnormalities to exclude chromosomal abnormality. The prognosis in patients with double outlet right ventricle depends on the severity of associated lesions, and the haemodynamic disturbances may be extremely variable. Clinical presentation is influenced by the presence or absence of pulmonary stenosis, the position of the ventricular septal defect in relation to the great arteries, and other associated major defects—for example, left ventricular outflow obstruction, mitral

valve abnormalities, and aortic arch abnormalities such as coarctation, hypoplasia, or even complete interruption.

Patients with the abnormalities described in the fetus in this report tend to present early in life and, clinically, may resemble patients with complete transposition and ventricular septal defect since the haemodynamic effects are similar.

Franks and Lincoln studied 46 patients from the Brompton Hospital who underwent surgical correction of double outlet right ventricle between April 1973 and April 1981.⁸ The patients were subdivided into groups according to the position of the ventricular septal defect. Of the 12 patients with subpulmonary ventricular septal defect, five had additional abnormalities. The overall mortality in this group was 80%. Palliation alone carried a mortality of 36%, and in the patients without significant pulmonary stenosis was not always possible. In patients with subpulmonary defects systemic saturation is usually low and pulmonary banding may reduce this still further to unacceptable levels.

The detection of serious fetal cardiac abnormalities allows the option for termination of pregnancy^{9 10} if they are diagnosed early enough in gestation, and the parents in our case requested this option after being told of the poor prognosis.

Ideally, scanning of fetuses at risk for structural cardiac defects should be performed between 17 and 24 weeks' gestation. During this period of pregnancy the heart is large enough for adequate visualisation, and there is enough amniotic fluid surrounding the fetus to provide a good ultrasonic window. In the present case optimal imaging of the fetal heart was possible only at 22 weeks' gestation because of maternal obesity.

When congenital heart disease is diagnosed later in pregnancy or when the defect is considered amenable

to surgery, or if the parents choose that the pregnancy should continue, steps can be taken to ensure optimal timing of delivery and immediate postnatal care in the paediatric cardiology unit.

We thank Dr C E Essed (Erasmus University, Rotterdam) for performing the necropsy and the Dutch Prevention Fund for funding this work.

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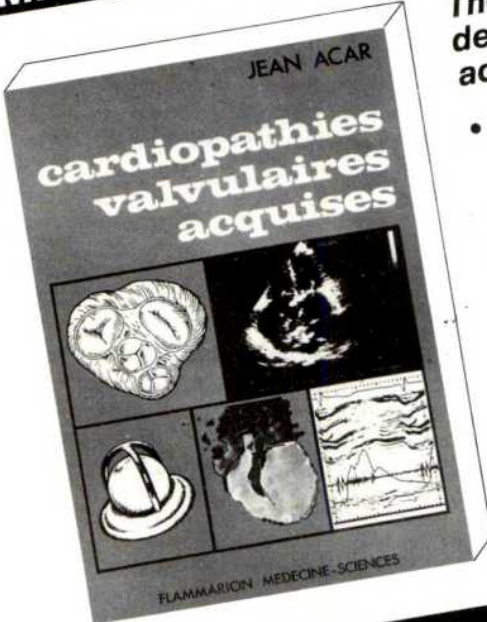
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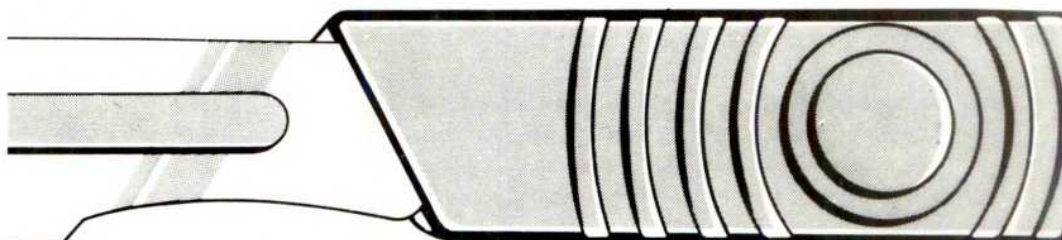


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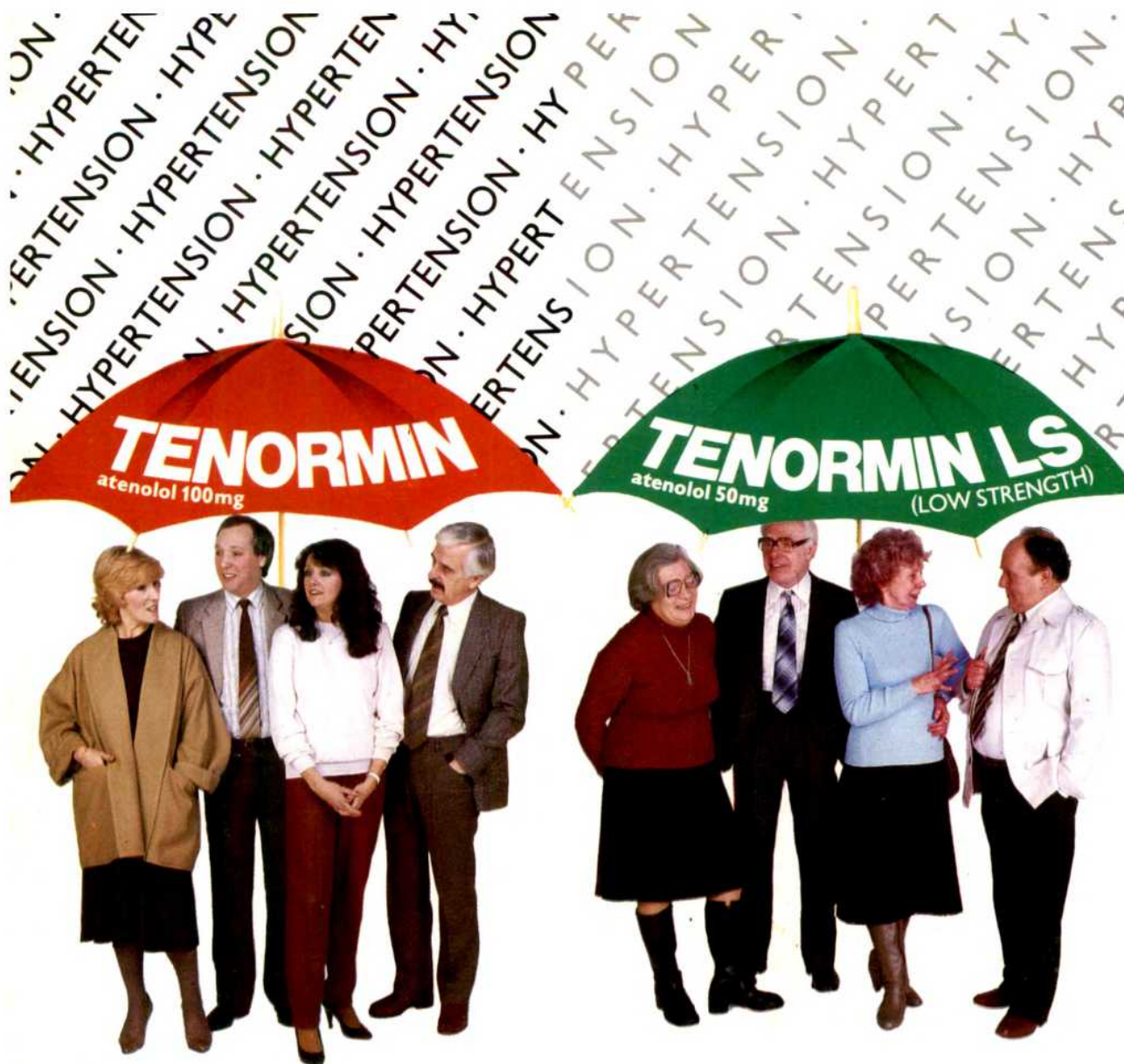
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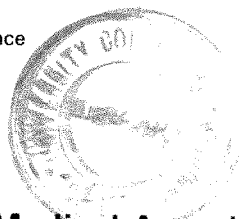
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- Bleeding complications of intracoronary fibrinolytic therapy in acute myocardial infarction: assessment of risk in a randomised trial *F W A Verheugt, M J van Eenige, J C J Res, M L Simoons, P W Serruys, F Vermeer, D C A van Hoogenhuyze, P J Remme, C de Zwann, F Baer* 455
- Surgical versus non-surgical management of patients soon after acute myocardial infarction *R W Brower, P Fioretti, M Simoons, M Haalebos, E N R Rulf, P G Hugenholtz* 460
- Myocardial infarct size and mortality in diabetic patients *D J Gwilt, M Petri, P W Lewis, M Natrass, B L Pentecost* 466
- Classification of non-Q-wave myocardial infarction according to electrocardiographic changes *H Ogawa, K Hiramori, K Haze, M Saito, T Sumiyoshi, K Fukami, Y Goto, M Ikeda* 473
- Reciprocal ST depression in acute myocardial infarction *O Odemuyiwa, I Peart, C Albers, R Hall* 479
- Characteristics of episodes of ST elevation or ST depression during ambulatory monitoring in patients subsequently undergoing coronary angiography *T von Arnim, B Höfling, M Schreiber* 484
- Bypass grafting to the right coronary artery with and without endarterectomy: patency at one year *P H Kay, N Brooks, P Magee, M F Sturridge, R K Walesby, J E C Wright* 489
- Quantification of intracardiac shunts by gold-195m, a new radionuclide with a short half life *D L Stone, R W Barber, O J M Ormerod, M C Petch, E P Wraight* 495
- Mitral valve prolapse, aortic compliance, and skin collagen in joint hypermobility syndrome *C E Handler, A Child, N D Light, D E Dorrance* 501
- Exercise radionuclide ventriculography in children: normal values for exercise variables and right and left ventricular function *M D Parrish, R J Boucek Jr, J Burger, M F Artman, C L Partain, T P Graham Jr* 509
- Diagnosis and natural history of Ebstein's anomaly *D J Radford, R F Graff, G H Neilson* 517
- Spectrum of congenital heart disease detected echocardiographically in prenatal life *L D Allan, D C Crawford, R H Anderson, M Tynan* 523
- Descending aortography with balloon inflation: a technique for evaluating the size of persistent ductus arteriosus in infants with large proximal left to right shunts *P S Rao* 527
- Asymmetric septal hypertrophy and hypothyroidism in children *D I Altman, J Murray, S Milner, R Dansky, S E Levin* 533
- Cardiac hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism—an association *C Symons, F Fortune, R A Greenbaum, P Dandona* 539
- Hypertrophic cardiomyopathy associated with a mitochondrial myopathy of voluntary muscles and congenital cataract *R C A Sengers, A M Stadhouders, E van Lakwijk-Vondrovicova, K Kubat, W Ruitenbeek* 543
- Case report
Chylopericardium: a rare complication of a Waterston shunt *J R L Hamilton, H C Mulholland, J Cleland* 548
- Correspondence 550
- Notices 556



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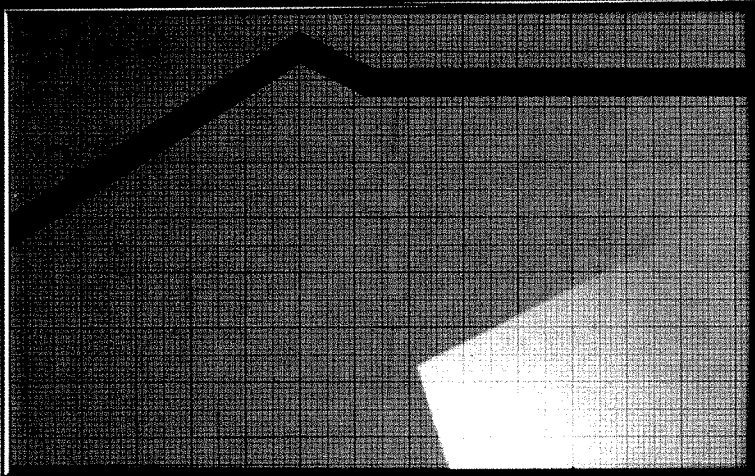
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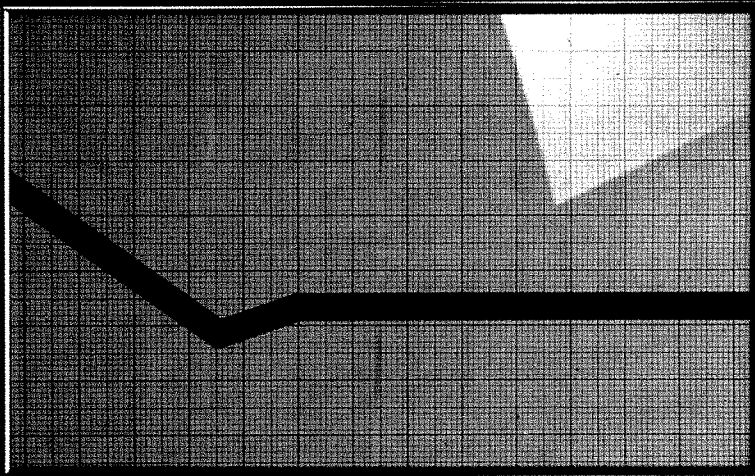
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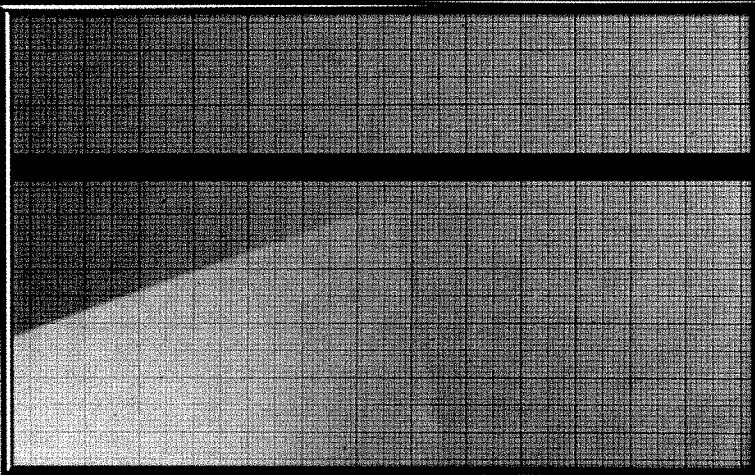
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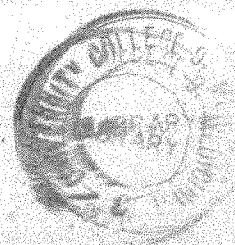
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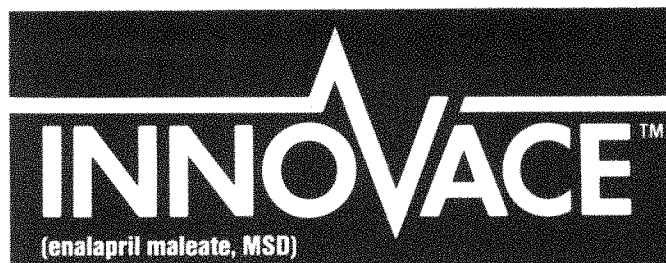
without increasing heart rate,² reduces both pre-load and after-load, and has both arterial and venodilating properties.¹

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DOSAGE

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CONTRA-INDICATIONS

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Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of 'Innovace' and their renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Some hypertensive patients, with no apparent pre-existing renal disease, have developed minor and usually transient increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required.

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DRUG INTERACTIONS

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SIDE EFFECTS

Generally well tolerated. Most side effects mild and transient, and have not required discontinuation of therapy. Most frequently: dizziness, headache, fatigue, asthenia. Others include hypotension, orthostatic hypotension, nausea, diarrhoea, muscle cramps, rash, cough, dysgeusia; and angioneurotic oedema. With minor and transient rises in blood urea or creatinine, dosage reduction and discontinuation of 'Innovace' and/or the diuretic may be required.

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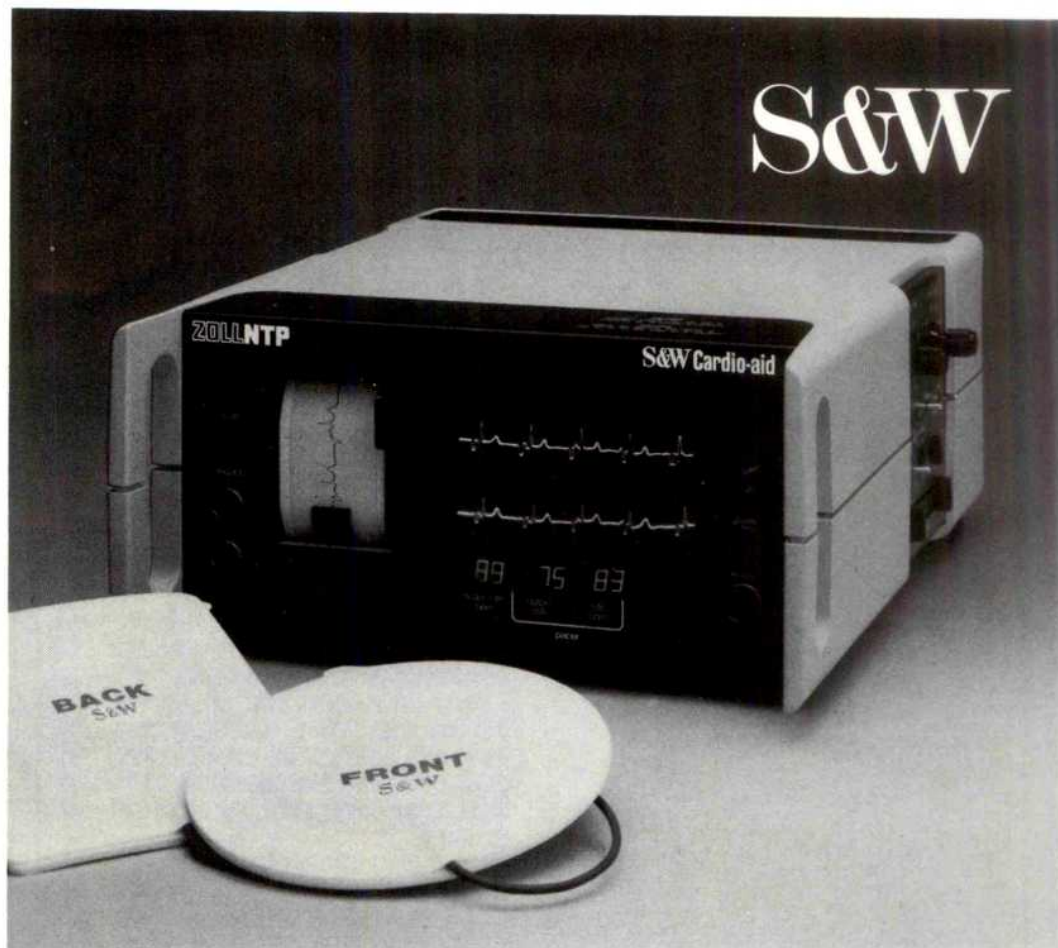
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1. Sharpe, D. N., *et al.*, *Circulation* 70, 1984, 2, 271.
2. Gomez, H. J., *et al.*, *Journal of Hypertension* (in press).
3. Kjekshus, J. K., *Scandinavian Journal of Urology and Nephrology*, 1984, Suppl. 79, p.115.





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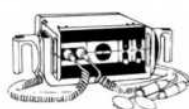
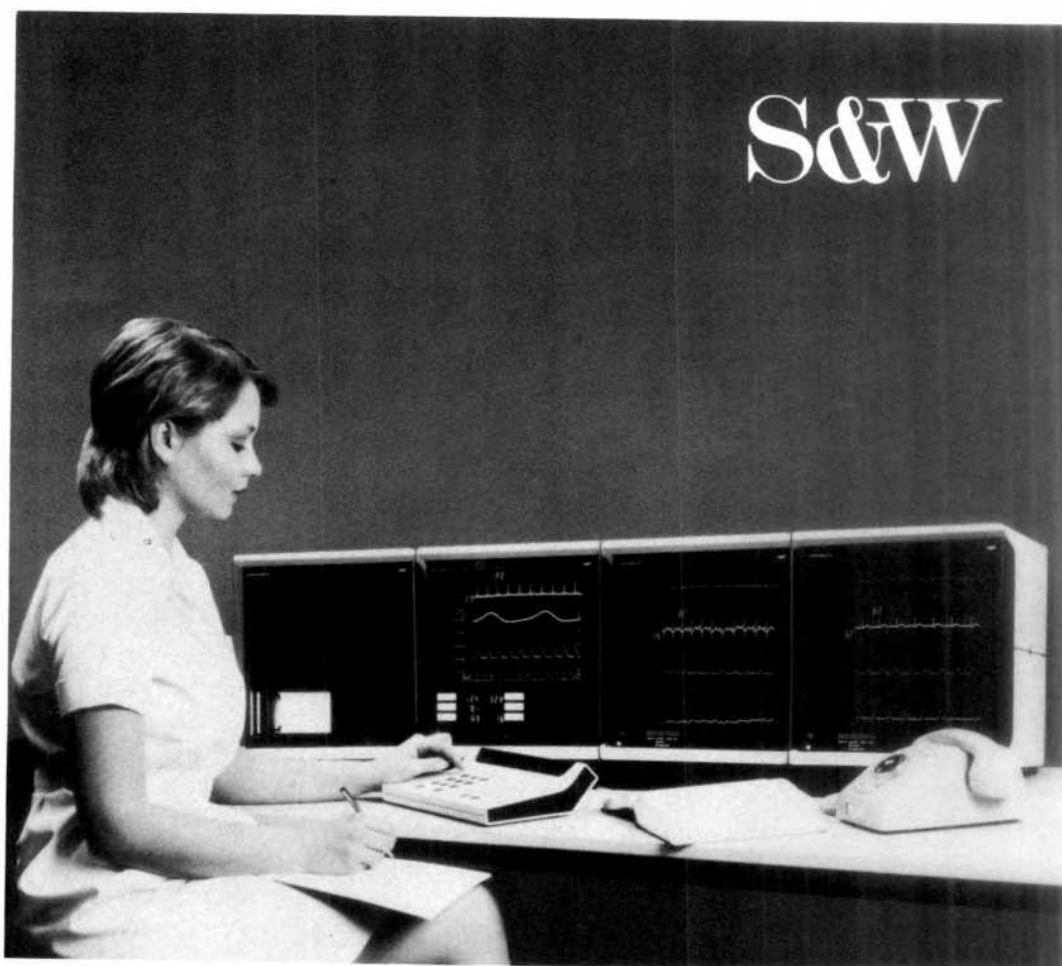
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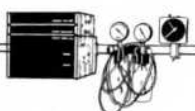




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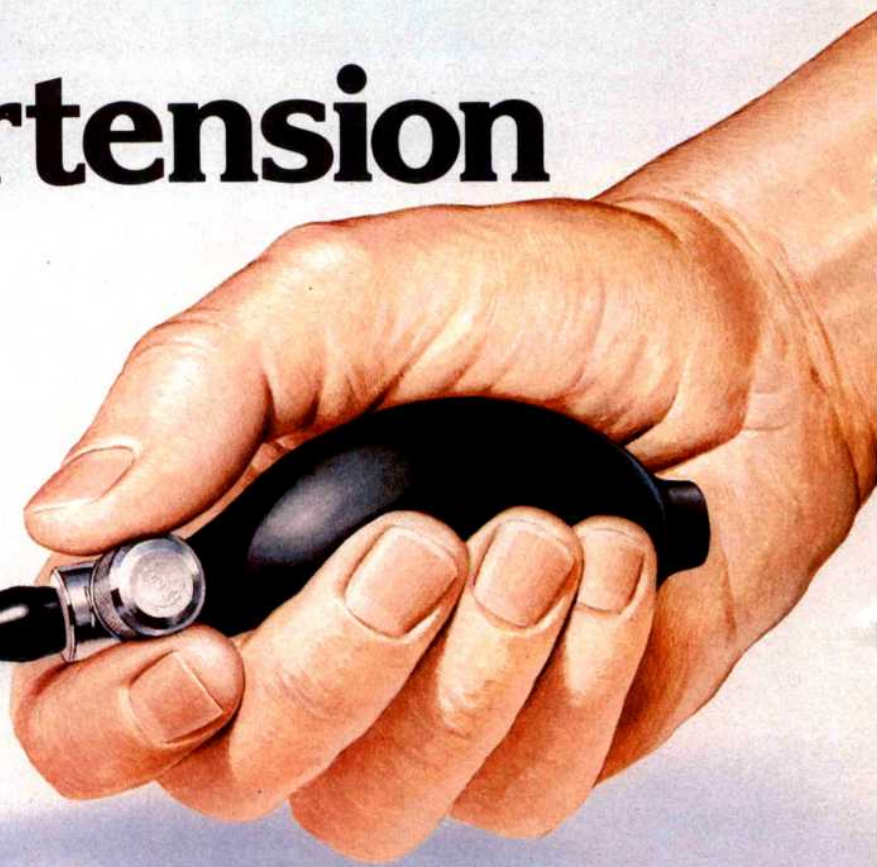
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Prescribing Information.

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Adalat Retard is not a beta-blocker and therefore gives no protection

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withdrawal should be by gradual reduction of the dose of beta-blocker,

preferably over 8-10 days. Adalat Retard may be used in combination with

beta-blocking drugs and other anti-hypertensive agents, but the possibility of

an additive effect resulting in postural hypotension should be borne in mind. Adalat

Retard will not prevent possible rebound effects after cessation of anti-hypertensive

therapy. Adalat Retard should be used with caution in patients whose cardiac reserve is

poor. Ischaemic pain has been reported in some patients, commonly within 30 minutes of

the introduction of nifedipine therapy. Patients experiencing this effect should discontinue

nifedipine. The use of nifedipine in diabetic patients may require adjustment of their control.

The antihypertensive effect of nifedipine can be potentiated by simultaneous administration with

cimetidine. There are no other known drug incompatibilities. Gravitational oedema associated with

increased capillary permeability has been reported. **Side Effects:** Adalat Retard is well tolerated. Minor

side-effects, usually associated with vasodilatation are mainly headache, flushing and lethargy. These are

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of 100. **Daily Treatment Cost:** 39p. **Product Licence Number:** Adalat Retard UK: PL0010/0078.



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Bleeding complications of intracoronary fibrinolytic therapy in acute myocardial infarction

Assessment of risk in a randomised trial

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SUMMARY The risk of bleeding associated with intracoronary infusion of streptokinase in acute myocardial infarction was determined in a randomised controlled trial containing 302 patients under the age of 70. Intracoronary streptokinase infusion was given to 152 patients and 150 patients were treated conventionally. Bleeding was seen in 24 (16%) patients in the streptokinase group and in two of the conventionally treated patients. Bleeding was most common (28%) in patients over the age of 60 years. The groin was the site of bleeding in all patients except one. In the first 48 hours after admission the haematocrit in streptokinase treated patients with manifest bleeding fell by 0.07 (0.04) (mean (SD)). The fall in haematocrit in the streptokinase treated patients without manifest bleeding was 0.05 (0.04) and in the conventionally treated patients it fell by 0.03 (0.04). Sixty six units of packed cells were transfused in the streptokinase group (50 units to those who bled); the control group required only 17 units. There were no deaths due to bleeding. The occurrence of bleeding and the fall in haematocrit in the streptokinase group correlated with the occurrence of systemic fibrinolysis but not with the dose of streptokinase given.

Thus, in about 15% of patients treatment with intracoronary streptokinase resulted in significant non-fatal bleeding from the femoral puncture site that required substantial transfusion support. Furthermore, there was a significant drop in haematocrit in patients without manifest bleeding. These results emphasise the need for more specific fibrinolytic agents.

Streptokinase is an effective thrombolytic agent in arterial and venous thrombotic disease.^{1,2} It can, however, produce massive, and potentially fatal bleeding due to systemic breakdown of fibrinogen and other clotting factors. Techniques of selective intra-arterial administration have been developed in an attempt to prevent such bleeding.

Intracoronary infusion of streptokinase in acute myocardial infarction has been shown to reduce infarct size,^{3,4} and preservation of left ventricular function^{4,5} and improvement in six month mortality⁴ have been reported. Although selective

thrombolysis with low dose streptokinase was very effective in achieving reperfusion of occluded coronary arteries, systemic fibrinolysis was common.⁶⁻⁹ The combination of intra-arterial instrumentation and systemic fibrinolysis when streptokinase is given by the intracoronary route may promote serious bleeding complications in acutely ill patients with myocardial infarction.

We analysed the risk of bleeding associated with intracoronary streptokinase treatment in acute myocardial infarction in a randomised multicentre study.

Patients and methods

The following four hospitals participated in a multicentre study in the Netherlands: Thoraxcenter, Dijkzigt Hospital, Rotterdam; Free University

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Accepted for publication 12 July 1985

Hospital, Amsterdam; Zuiderziekenhuis, Rotterdam; and Annadal Hospital, Maastricht. Between May 1981 and December 1983, 302 patients who met the following criteria entered the trial: (a) typical history and symptoms of acute myocardial infarction within 4 hours of admission; (b) electrocardiographic changes typical of acute transmural myocardial infarction (that is, ST elevation in the standard leads of ≥ 0.1 mV or ST elevation of ≥ 0.2 mV in the precordial leads); (c) age ≤ 70 years; (d) absence of earlier streptokinase treatment, coronary bypass operation in the area infarcted at admission, recent trauma, prolonged cardiac massage, menorrhagia, pregnancy, unconsciousness, active gastric ulcer, haematuria, or stroke. Data on the patients at admission are given in Table 1. After admission to the study the patients were randomly allocated to either intracoronary streptokinase treatment ($n=152$) or conventional treatment ($n=150$). Informed consent was obtained from patients randomised to the streptokinase group. They underwent coronary arteriography by the transfemoral (Judkins) route through a French 7 introducer sheath. An intravenous bolus injection of 250 mg acetylsalicylic acid, 100 mg hydrocortisone, and 5000 units of heparin was then given. In patients in whom the infarct related coronary artery was occluded, intracoronary streptokinase was infused at a rate of 4000 units per minute. Coronary arteriography was repeated every 15 minutes to check whether reperfusion had taken place. After reperfusion, if any, the infusion of streptokinase was continued for at least 15 minutes. Intracoronary streptokinase infusion was limited to a maximum of 60 minutes corresponding to a maximum dose of 250 000 units. When the infarct related coronary artery was patent on the first arteriogram, the artery was perfused with 4000 units of streptokinase per minute for 15 minutes. A left ventricular cine-

angiogram was then obtained and left ventricular pressures were recorded. The arterial catheter was removed and the femoral artery introducer sheath remained in place for 24–48 hours.

A Swan-Ganz catheter was introduced by femoral (only in the streptokinase patients), subclavian, jugular, or brachial vein puncture by a French 8 introducer sheath and the catheter remained in the pulmonary artery for 24 to 48 hours. Heparin infusion of 10 000–20 000 units per 24 hours and coumadin were started in the coronary care unit. Heparin infusion was stopped when the partial thromboplastin time exceeded 120 sec.

Patients in the control group underwent conventional treatment and had haemodynamic monitoring with a Swan-Ganz catheter in the same way as the patients in the streptokinase group. Anticoagulation with heparin and coumadin was identical to that given to patients in the streptokinase group. In 13 patients (9%) allocated to streptokinase treatment, catheterisation was not performed because of technical difficulties or because the patient refused. Three patients (2%) allocated to conventional treatment had intracoronary infusion of streptokinase during the acute phase. The results were analysed on the basis of intention to treat.

Venous blood samples were taken at admission and at 3, 6, 12, 18, 24, 36, and 48 hours after admission for laboratory tests including haemoglobin concentration and haematocrit. Standard medical care, including analgesics, diuretics, and inotropic support, was given to all patients.¹⁰ The occurrence of bleeding, thrombosis, pulmonary embolism, recurrent angina and infarction or both, left ventricular failure, and arrhythmias was recorded. Blood transfusions were given according to the instructions of the consulting physicians. Haemoglobin concentrations which were below 7.0 mmol/l (11.2 g/dl) at admission or during the first 48 hours after acute myocardial infarction were regarded as an indication for blood transfusion.

Bleeding was defined as the occurrence of haematoma, haemoptysis, haematemesis, melaena, haematuria, or an intracranial event within 48 hours of admission. Swelling was regarded as an essential feature of the diagnosis of haematoma at the puncture site. To estimate the change in haematocrit during routine heart catheterisation, we studied 43 other patients, aged ≤ 70 years, undergoing elective coronary angiography and left ventricular cine-angiography because of chest pain. The haematocrit was determined 24 hours before and 24 hours after the procedure. The arterial catheterisation procedure was identical to the procedure used in the study, except that streptokinase, acetylsalicylic acid, and hydrocortisone were not infused. The arterial

Table 1 Characteristics mean (SD) of patients before randomisation

	Streptokinase	Control
No of patients	152	150
Sex (% male)	82	85
Age (yr)	54.6 (9.3)	54.5 (8.9)
Use of oral anticoagulants	11	6
Use of antiplatelet drugs	0*	6*
Resuscitated	4	2
Systolic blood pressure (mm Hg)	133.1 (28.2)	133.3 (27.1)
Diastolic blood pressure (mm Hg)	85.3 (17.2)	87.8 (17.5)
Heart rate (beats/min)	72.9 (15.2)	73.1 (17.2)
Haemoglobin (mmol/l)	9.2 (0.9)	9.2 (0.9)
Haematocrit	0.44 (0.04)	0.44 (0.04)
Lactate dehydrogenase (U/l)	249 (105)	245 (96)

* $p < 0.05$

Conversion: Haemoglobin: 1 mmol/l = 1.6 g/dl.

Lactate dehydrogenase: 1 U/l = 16.67 nkat/l.

catheter sheath was removed immediately after the patients had received 50 mg of protamine sulphate intravenously.

STATISTICAL ANALYSIS

The results were analysed by Student's *t* test for either unpaired or paired data, or by the χ^2 test for frequency distribution analysis.

Results

CHARACTERISTICS OF PATIENTS BEFORE RANDOMISATION

Apart from the more frequent use of anti-platelet drugs in the control group there were no significant differences between the two groups before randomisation (Table 1).

BLEEDING, SITE OF BLEEDING, AND TRANSFUSION REQUIREMENT

Twenty four patients (16%) in the streptokinase group had manifest bleeding which caused groin haematomas in all of them. None of this group had bleeding at other sites. Two patients (1%) on conventional treatment had bleeding—one groin haematoma and one haematoma at a venepuncture site on the forearm. There were no deaths from bleeding in either group. Patients in the streptokinase group needed 66 units of packed cells compared with 17 units in the control group ($p < 0.0001$). In the streptokinase group 50 units of packed cells were given to patients with manifest bleeding (16 patients) and 16 units to patients without manifest bleeding (eight patients). Analysis of the characteristics of all patients before randomisation (Table 1) in relation to these results showed that only age was of predictive value. There was bleeding in 15 (28%) of the 53 patients aged ≥ 60 . Only nine (10%) of those aged < 60 had bleeding complications. Thirty two per cent of the patients with bleeding complications and 16% of those without were female. This difference is not statistically significant. The control group required transfusions of 17 units of packed cells to

eight patients including one with manifest bleeding. Table 2 summarises these results.

FALL IN HAEMATOCRIT

We excluded results from 98 patients (56 allocated to streptokinase and 42 to conventional treatment) from the analysis because haematocrit values were missing at admission or during the first 48 hours (82 cases), because patients allocated to streptokinase had received conventional treatment (13 cases), and because intracoronary streptokinase had been given to three conventionally treated patients. Haematocrits at entry and the lowest values observed in the first 48 hours after entry were recorded in the remaining 204 patients (97 in the treated group and 107 in the controls). Characteristics before randomisation were no different in this subgroup than in the total group as defined in Table 1. The mean (SD) fall in haematocrit was 0.05 (0.04) in the streptokinase treated group and 0.03 (0.04) in the conventionally treated group.

Table 3 shows the characteristics, the dose of streptokinase, and the fall in haematocrit in these patients in relation to bleeding complications. There were no differences in the characteristics before randomisation among the three groups. As expected, in the streptokinase group there was a larger fall in haematocrit in the patients with manifest bleeding than in those without. The fall in haematocrit in the latter group, however, is still significantly higher than in the controls, indicating that there may have been occult bleeding without manifest bleeding in the streptokinase treated patients. The dose of streptokinase was similar in patients with manifest bleeding complications and in those without.

SYSTEMIC FIBRINOLYSIS

Venous fibrinogen concentrations were measured before and immediately after intracoronary streptokinase infusion in 24 patients in the streptokinase group (four patients with and 20 without manifest bleeding). Systemic fibrinolysis was judged to have occurred when the fibrinogen concentration

Table 2 Frequency of bleeding and transfusion requirement in all patients

	Streptokinase		Control	
	Bleeding	Non-bleeding	Bleeding	Non-bleeding
No of patients	24*	128	2	148
Sex (% male)	71	84	0	86
Age over 60 years	15 (63%)***	38 (30%)	2 (100%)	37 (25%)
Transfusions (units)	50**	16	4	13
Patients transfused	16 (67%)	8 (6%)	1 (50%)	7 (5%)

* $p < 0.0001$, vs control group.

** $p < 0.01$, vs control group.

*** $p < 0.01$, vs non-bleeders in the streptokinase group.

Table 3 Fall in haematocrit, dose of streptokinase, and transfusion support in 204 patients (mean (SD))

	Streptokinase group		Controls
	Bleeding	Non-bleeding	
No of patients	18	79	107
Baseline haematocrit	0.42 (0.02)	0.45 (0.04)	0.44 (0.04)
Fall in haematocrit	0.07 (0.04)	0.05 (0.04)	0.03 (0.04)
Dose of streptokinase ($\times 10^3$ units)	234 (58)	218 (80)	0
Transfusions (units)	40	6	11
Patients transfused (no)	11 (61%)	3 (4%)	6 (6%)

* $p < 0.001$ vs control group.

dropped to 50% or less of the original value.

Systemic fibrinolysis occurred in 19 (79%) of the 24 patients tested. The fall in haematocrit (0.05 (0.03)) in the patients without systemic fibrinolysis was greater than the fall in those with fibrinolysis (0.01 (0.03), $p < 0.05$). There was manifest bleeding in four patients (21%) with systemic fibrinolysis and in none of the patients without systemic fibrinolysis.

DOSE OF INTRACORONARY STREPTOKINASE AND FALL IN HAEMATOCRIT

There was no correlation between the dose of intracoronary streptokinase given to the 97 patients shown in Table 3 and the fall in haematocrit (Figure).

HAEMATOCRIT BEFORE AND AFTER ELECTIVE CATHETERISATION

There was no change in haematocrit in patients

undergoing elective heart catheterisation (0.45 (0.02) before and 0.45 (0.04) 24 hours after catheterisation).

Discussion

Although controlled trials have not confirmed the efficacy of intravenous streptokinase treatment in acute myocardial infarction,^{11,12} they have shown that a dose of 2.5 million units in 24 hours may safely be given. There were reports of non-fatal bleeding complications in 0–25% of patients but they did not require transfusion.^{11–13} The effective intracoronary dose of streptokinase is quite low but arterial puncture and instrumentation themselves increase the risk of bleeding. The reported frequency of haemorrhagic complications associated with intracoronary streptokinase varies from 0% to 23%.^{3,4,14,15} Isolated reports of bleeding after intracoronary streptokinase¹⁶ may merely reflect normal complications of myocardial infarction. Haemorrhagic infarction^{17,18} with or without ventricular rupture can occur without fibrinolytic treatment.

We found bleeding in 16% of patients treated with intracoronary streptokinase. Bleeding occurred exclusively at the femoral puncture site and substantial transfusion support was necessary. Bleeding resulted in a large drop in haematocrit.

The haematocrit usually falls to 0.02 in the first few days after acute myocardial infarction.¹⁹ But the fall in patients treated with streptokinase (even in those without manifest bleeding) was significantly higher than that in the control group. This suggests that there was occult bleeding in the group given streptokinase. Such bleeding is minor, of unknown origin, and has no clinical consequences. It is not the result of standard anticoagulation (intravenous heparin and oral coumadin), since control patients on the same regimen had a significantly smaller fall in haematocrit. Nor can it be attributed to venous catheterisation because most patients had this procedure. Furthermore arterial catheterisation per se does not necessarily cause a drop in haematocrit, since in our hands elective catheterisation did not

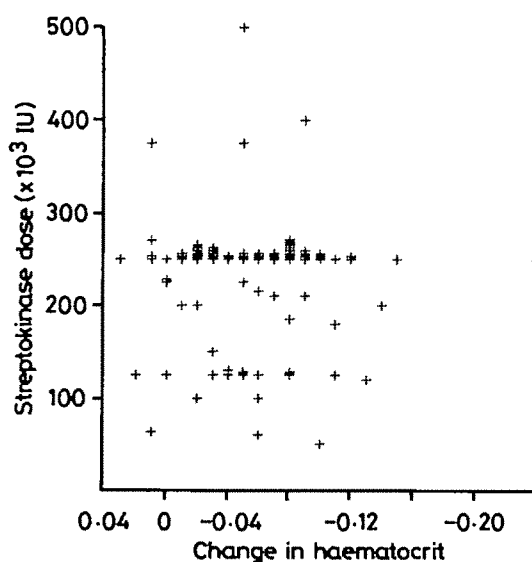


Figure Fall in haematocrit and dose of intracoronary streptokinase in 97 patients.

change haematocrit. Though it is a time consuming procedure that is unpleasant for the patient, there are likely to be benefits associated with the low dose of streptokinase used in selective infusion. Systemic fibrinolysis, however, is often seen in intracoronary streptokinase treatment⁶⁻⁸ as well as in intravenous streptokinase infusion, and this complication has even been correlated with the success of the procedure.²⁰⁻²² We found systemic fibrinolysis in 80% of patients screened. The fall in haematocrit was higher in patients with systemic fibrinolysis than in those without. This confirms the correlation between bleeding and systemic fibrinolysis.¹⁴ Bleeding in patients undergoing intracoronary streptokinase infusion was apparently caused by streptokinase induced systemic fibrinolysis together with the arterial catheterisation and the use of intravenous acetylsalicylic acid and hydrocortisone. Bleeding was not related to the dose of streptokinase given, as has already been shown by others.¹⁴

CLINICAL IMPLICATIONS

There is a definite risk of non-fatal major arterial bleeding associated with intracoronary streptokinase treatment. This is attributable to the combined use of streptokinase with a catheterisation procedure. Bleeding was three times more common in patients over the age of 60 than in younger patients and tended to be more common in females. The appearance of a groin haematoma after intracoronary streptokinase treatment indicates important bleeding and transfusion support was required by about 70% of patients with this complication. The use of more specific fibrinolytic agents such as tissue plasminogen activator,²³ might avoid these complications.

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Surgical versus non-surgical management of patients soon after acute myocardial infarction

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SUMMARY Of 510 patients admitted to hospital with acute myocardial infarction, 34 had coronary artery bypass grafting before discharge (6-43 days (median 20) after infarction). The patients who were given grafts generally had a smaller infarction with less functional impairment than the 476 patients who were not. The outcome of coronary artery bypass grafting was investigated in a retrospective matched pair study. Patients were matched on the basis of the presence of post-infarction angina, left ventricular ejection fraction, location of the infarction, peak creatine kinase activity, Killip clinical class, and severity of coronary disease with 34 patients who were given medical treatment only. At one year follow up fewer of the operated patients had symptoms than did the matched non-operated patients. Survival at one year in the operated and non-operated groups respectively was 94% vs 91%; angina within one year occurred in 3% vs 68%; congestive heart failure in 3% vs 6%; and 0% vs 32% were referred for later bypass grafting or coronary angioplasty.

It is concluded that coronary artery bypass grafting can be performed safely soon after myocardial infarction provided that left ventricular function is not seriously compromised. Such treatment is more effective than medical treatment for relief of angina during the first year after infarction.

Referral for coronary artery surgery early after acute myocardial infarction presents a dilemma to the cardiovascular team. It has long been maintained that surgery at this stage carries substantial operative risks; recent reports, however, suggest that such estimates of operative mortality and complications may be unduly pessimistic.¹⁻³ DeWood *et al* and Berg *et al* have reported that surgery can be safely performed in the acute phase of infarction with excellent results.¹⁴ When pharmacologically uncontrolled angina indicates the likelihood of further deterioration, the indication for surgery is clear, especially since it may be possible to salvage the jeopardised myocardium. The possibility that surgery will improve long term survival or prevent reinfarction in this group of patients, however, has not been proven.

For the past few years we have referred patients

for coronary bypass surgery when recurrent angina was refractory to pharmacological treatment, in some patients soon after acute myocardial infarction and in others when angina was induced by mild exertion and associated with severe coronary lesions. It has been our impression that this could be done at low risk and with good long term results.

We have compared results in a group of patients operated on soon after infarction with results in all other patients seen over the same period who received only pharmacological treatment. We have also compared them with a matched pair series of patients at similar risk and with similar symptoms who were not operated on. Over a one year follow up we compared mortality, reinfarction, late referral to bypass surgery or coronary angioplasty, and recurrence of complaints.

The sole criterion for inclusion in the surgery group was that the patient had isolated coronary artery bypass grafting soon after an acute infarction and before hospital discharge. Most had angina pectoris at rest that was resistant to intensive medical treatment. There are always exceptional cases, how-

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Accepted for publication 22 July 1985

ever, generally those with angina during mild exertion or advanced proximal lesions or both. In this study we have chosen to include all cases referred to surgery before hospital discharge after an acute myocardial infarction.

Patients and methods

Myocardial infarction was diagnosed when at least two of the following were present: typical prolonged chest pain lasting at least 45 minutes; evolving QR complexes or Q waves of more than 0.04 s duration with ST and T wave changes in the case of transmural infarction, or T wave inversion or ST depression persisting for at least 24 hours without loss of the R wave or development of new Q waves in the case of non-transmural infarction; a typical rise and fall of total creatine kinase with a peak activity greater than 100 IU/l (twice the upper limit for normal in our clinic).

From March 1981 to February 1983 there were 529 admissions with acute infarction. Hospital treatment followed the guidelines described by Simoons *et al.*⁵ Four cases were referred for surgery because of mitral valve incompetence, ventricular septal defect, or free wall ventricular rupture, and fifteen were treated by elective percutaneous transluminal angioplasty before discharge. These nineteen patients were excluded.

Of the remaining patients, 34 had coronary surgery during the admission for myocardial infarction and 476 did not. In 27 patients the indication for operation was persistent angina pectoris at

rest, refractory to medical treatment including beta blockers, calcium antagonists, and nitrates. Three of these patients were in Killip class III or IV during the acute phase of infarction. No patient was in severe heart failure or cardiogenic shock at the time of operation. The seven other patients did not have persisting angina at rest; three of them had angina during mild exertion and they were found to have severe proximal lesions, and four had severe proximal lesions in the infarct related artery after attempted intracoronary thrombolysis with streptokinase. Table 1 summarises the clinical data at entry to the trial. The coronary score⁶ was 15.5 (8.8) (mean (SD)), three patients were classified as having proximal three vessel disease, none had exclusively distal vessel disease.

Seventy three (15%) of the 476 patients who were not referred to surgery also had post-infarction angina, but they were not offered surgery for various reasons: angina became responsive to medication; there were contraindications to surgery because of severe non-cardiac disease; some refused surgery; and in a few the coronary anatomy was not suitable. Poor left ventricular function was not regarded as a contraindication to coronary bypass operation.

A subgroup of 34 non-operated patients was matched to the operated patients on the basis of age, presence of angina during the hospital stay, Killip class, left ventricular ejection fraction (radionuclide ventriculography) at discharge or before surgery, location of the infarction, peak serum creatine kinase activity, and anatomical severity of coronary artery disease (greater than 50% diameter stenosis, coded

Table 1 Key prognostic variables used to select matched pairs from the larger series of non-operated patients to match the group of operated patients

Variable	Operated	Matched non-operated	p	All non-operated	p
No. of cases	34	34	—	476	—
Age (years)	60.7 (6.1)	55.5 (8.9)	0.01	58.3 (11.6)	NS
Post-infarction angina at rest	27 (79%)	25 (74%)	NS	73 (15%)	0.0001
Ejection fraction	0.48 (0.14)	0.49 (0.11)	NS	0.45 (0.16)	*
	(31 cases)	(34 cases)		(358 cases)	
Location of MI:			NS		0.025
Transmural anterior	9 (26%)	10 (29%)		189 (40%)	
Transmural inferior	10 (29%)	9 (26%)		177 (37%)	
Non-transmural	15 (44%)	15 (44%)		102 (21%)	
Undefinable/unknown	0	0		8	
Peak serum CK (IU/l)	420 (390)	420 (320)	NS	610 (530)	0.05
Killip class:			NS		0.025
I	25 (74%)	25 (74%)		278 (58%)	
II	6 (18%)	6 (18%)		113 (24%)	
III or IV	3 (9%)	3 (9%)		85 (18%)	
Anatomical severity:			NS		*
1 or 2 vessel disease	15 (44%)	18 (53%)		111 (23%)	
3 vessel or left main vessel disease	19 (56%)	16 (47%)		43 (9%)	
Unavailable	0	0		322 (68%)	

Data are reported as events and percentage of cases or as mean (SD). Statistical comparisons: non-operated *vs* operated; NS, difference not significant at the 0.05 level.

*No statistical comparison because large numbers of entries were missing.
MI, myocardial infarction; CK, creatine kinase.

as (a) one or two vessel disease or (b) three vessel disease or worse) (Table 1). Mean (SD) coronary score⁶ was 12.5(6.5), one case was classified as having proximal three vessel disease and five cases having exclusively distal vessel disease.

Medication in the operated patients (at referral to surgery) was compared with that in the non-operated matched pairs: beta blockers in 85% of operated *vs* 80% non-operated, calcium antagonists in 85% *vs* 60%, nitrates in 85% *vs* 70%, digoxin in 18% *vs* 15%, and diuretics in 29% *vs* 33%. Treatment at discharge for all 476 non-operated patients included beta blockers in 44%, calcium antagonists in 19%, nitrates in 33%, digoxin in 25%, and diuretics in 38%. The median duration from onset of the infarction to operation was 20 days (range 6 to 43 days); 97% were operated on within 35 days. For those patients referred for operation, treatment with analgesics and sedatives had already been started, hence additional premedication was usually not required. Intravenous fentanyl 15 µg/kg was used for induction of anaesthesia and 0.1 mg/kg pancuronium was given to facilitate intubation. Treatment with intravenous glyceryl trinitrate and inotropics was determined on the basis of arterial pressure monitoring and in principle drug treatment continued until extracorporeal circulation was established. The patient was ventilated with a servo-ventilator with a mixture of oxygen and nitrous oxide (40:60). Additional intravenous fentanyl and possibly pancuronium were given as required before sternotomy and later during operation.

Coronary artery bypass grafting was performed with moderate systemic hypothermia (28°C) and cardioplegic arrest in combination with topical cooling by means of a saline solution (4°C). Cardioplegic arrest was accomplished by use of at least 500 ml of St Thomas's solution (sodium chloride 91.6 mmol/l, potassium chloride 14.8 mmol/l, magnesium sulphate 1.2 mmol/l, magnesium chloride 15 mmol/l, potassium dihydrogen phosphate 1.2 mmol/l, calcium chloride 1.2 mmol/l, and hydrochloride pro-

caine 1.0 mmol/l). This was administered through the aortic root after cross clamping. If cross clamping lasted more than one hour after the initial infusion, cardioplegia was repeated every 60 minutes to maintain a flat electrocardiogram.

A jump graft was constructed with a saphenous vein graft to all coronary arteries which had stenosis of 50% or more. One sequential vein graft was routinely used and all distal anastomoses were made during cardioplegic arrest. The proximal anastomosis was made after removing the cross clamp during rewarming. The average revascularisation rate was 3.5 grafts per patient (6 cases with 5 grafts, 11 with 4, 10 with 3, and 7 with 2). Sinus rhythm usually returned spontaneously. The left ventricle was always vented by means of a left ventricular drain.

Ventilation in the postoperative period was continued until the patient awoke and was haemodynamically stable. Hypertension was treated with nitroprusside. The patient was extubated on the same day as operation or the next morning.

Results

Compared with the 476 non-operated cases, the 34 operated cases had a greater frequency of non-transmural infarction, were more often in Killip class I, and had lower mean peak serum creatine kinase values, indicating less myocardial damage from the acute infarction. The ejection fraction, however, appeared to be similar in both groups, but it was not known in 61 of 70 (87%) of patients who died in hospital compared with 60 of 444 (14%) hospital survivors. The mean (SD) ejection fraction of 0.45 (0.16) for non-operated cases, because it is derived from the group containing the larger fraction of deaths, may therefore overestimate the true ejection fraction for this group. Finally, the in-hospital mortality rate was 3% for operated cases *vs* 14% for all 476 non-operated cases (Table 2). All these

Table 2 Clinical information before discharge from hospital

Variable	Operated	Matched non-operated	p	All non-operated	p
No of cases	34	34	—	476	—
Males	27 (79%)	29 (85%)	NS	377 (79%)	NS
History of angina of more than 4 weeks	22 (65%)	11 (32%)	0.01	164 (34%)	0.0005
History of old MI	17 (50%)	17 (50%)	NS	145 (30%)	0.02
Wedge pressure (mm Hg) at admission	9.8 (6.1)	11.1 (4.5)	NS	13.3 (6.6)	0.05
Cardiac index in CCU at admission	3.1 (1.1)	2.8 (0.7)	NS	2.6 (0.8)	0.05
Systemic arterial pressure	119 (20)	126 (23)	NS	121 (25)	NS
Length of hospital stay	22 (10)	18 (15)	NS	12 (10)	0.0001
Recurrent MI in hospital	4 (12%)	3 (9%)	NS	24 (5%)	NS
Death in hospital	1 (3%)	1 (3%)	NS	69 (14%)	0.07

Data are reported as events and percentages of cases or as mean (SD). Statistical comparisons: non-operated *vs* operated; NS, difference not significant at the 0.05 level.
MI, myocardial infarction; CCU, coronary care unit.

results indicate that patients referred for coronary artery bypass grafts were generally in a better condition overall after their myocardial infarction than were the non-operated patients. Therefore some form of matching is required to obtain a meaningful comparison between the operated and non-operated patients.

The size of the infarction appeared to have a bearing on the timing of operation; when peak serum creatine activity was <400 IU/l the median delay from date of myocardial infarction to operation was 14 days compared with 26 days when creatine kinase was ≥ 400 IU/l.

One year survival in the operated cases was 94% compared with 91% in matched non-operated cases (Table 3). Two patients in the operated group died; both had had post-infarction angina and were in congestive heart failure in the acute phase of infarction. The first death, in a man aged 65, occurred in the perioperative period and 7 days after the infarction. He had an inferior infarction with peak serum creatine kinase activity of 530 IU/l, an ejection fraction of 0.37, and three vessel disease. Death was caused by low cardiac output syndrome. All grafts were found to be thrombosed. The second death, in a man aged 64, occurred 5 months after infarction and was caused by congestive heart failure. He had had an extensive inferior infarction with peak serum creatine kinase activity of 1595 IU/l.

There were three deaths in the matched non-operated group. The first occurred 26 days after infarction due to cardiac rupture in a 60 year old man (inferior infarction, peak serum creatine kinase activity 400 IU/l, ejection fraction 0.41, three vessel disease, and with congestive heart failure in the acute phase). This patient did not have post-infarction angina in the acute phase but the other two did. The second death occurred at 70 days due to progressive cardiac failure in a 50 year old man (anterior infarction, peak serum creatine kinase activity 1360 IU/l, ejection fraction 0.18, three vessel disease). The third death occurred at 67 days due to

congestive heart failure in a 67 year old man (anterior infarction, peak serum creatine kinase activity 130 IU/l, ejection fraction 0.24, history of previous infarctions, three vessel disease).

Among the survivors at one year (32 operated, 31 matched non-operated, and 356 non-operated cases) there were several highly significant differences. Cardiological events were infrequent in the operated cases; only one patient had angina and another had symptoms of congestive heart failure. Of the 356 survivors in the non-operated group, 143 reported angina by one year (43% of survivors), 57 had had an episode of congestive heart failure (16% of survivors), and 30 were eventually referred to coronary artery bypass graft surgery (8% of survivors). The comparison of operated survivors with the matched non-operated patients is even more striking. Of the 31 matched non-operated survivors, 23 (74%) had angina by one year (five with angina Killip class IV, six with class III, and twelve with class II) and 10 were referred for late coronary artery bypass surgery (32%). The frequency of recurrent infarction and congestive heart failure, however, is similar to that in the operated cases.

Since the indication for coronary artery bypass grafting shortly after an acute infarction is recurrent angina resistant to medical treatment, it is pertinent to ask whether these cases differ in any other important way from those without post-infarction angina. To avoid a selection bias, we considered only those patients who survived the first 72 hours after the acute event. Ninety eight patients presented with such post-infarction angina (21% of 472 patients surviving three days or more) (Table 4). There were no significant differences in the distribution of age, sex, or history of a previous infarction, although cases with recurrent angina do have a longer history of angina before the acute event. Ventricular function is virtually identical in the two groups as is one year survival. At discharge beta blockers, nitrates, and calcium antagonists were more frequently being given to patients with post-infarction angina.

Table 3 Follow up of patients after discharge from hospital

Variable	Operated	Matched non-operated	p	All non-operated	p
No. of cases	34	34	—	476	—
Death after discharge	1 (3%)	2 (6%)	NS	51 (11%)	NS
Survival at 1 year	32 (94%)	31 (91%)	NS	356 (75%)	0.02
Recurrent MI by 1 year	0 (0%)	0 (0%)	NS	27 (6%)	NS
Angina by 1 year	1 (3%)	23 (68%)	0.0001	153 (32%)	0.0001
CHF within 1 year	1 (3%)	2 (6%)	NS	57 (12%)	0.05
CABG within 1 year	0 (0%)	10 (29%)	0.001	30 (6%)	NS
PTCA within 1 year	0 (0%)	1 (3%)	NS	5 (1%)	NS

Data reported as events and percentage of cases. Statistical comparisons, non-operated vs operated; NS, difference not significant at the 0.05 level.

MI, myocardial infarction; CHF, congestive heart failure; CABG, coronary artery bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty.

Discussion

Earlier reports on the outcome of bypass operations performed soon after acute myocardial infarction were not encouraging. In 1974 Dawson *et al* reported a hospital mortality rate of 14.5% in 145 patients operated on within two months of an acute myocardial infarction and a rate of 38% in those operated within one week.⁷ At that time hospital mortality for elective coronary artery bypass graft surgery in patients without a recent myocardial infarction was 6.2% at the same hospital. Because this latter figure is considerably higher than that currently reported^{8,9} (less than 2% at most hospitals), it is likely that the surgical mortality for patients with acute infarction has also fallen, and, indeed, recent reports clearly demonstrate this fact. In 1985 Williams *et al* reported a hospital mortality rate of 2% in patients operated on within 30 days of infarction,² and Nunley *et al* reported a 3% operative mortality rate in those operated on within two weeks of infarction; this was in a subgroup of 66 patients with threatened extension of infarction.³ In our series the operative mortality is one case out of 34 (3%) while the one year survival (94%) accords with the recent reports mentioned above. The current operative mortality rate at our institution for all aortocoronary bypass surgery is 1.2% with a 5 year survival of 93.5%.¹⁰ While surgical mortality after acute infarction has apparently improved greatly over the past decade, it still falls somewhat short of the excellent results of elective surgery.

It should be borne in mind that our results are based on a retrospective study with all the limitations inherent in such an approach, and despite matching major differences remain between the two groups—these are responsiveness to medical treatment, unsuitable coronary anatomy for bypass surgery, and important non-cardiac disease. For example, five patients in the non-operated group had exclusively distal vessel disease whereas none of the operated group did.

There has been a substantial improvement in surgical technique and postoperative care since the early 1970s, and we agree with Nunley *et al*³ that current results do mitigate the concern about attempting an early operation in patients with post-infarction angina. Nevertheless, we should continue to exercise caution. Because the current policy generally excludes patients with extensive ventricular dysfunction, much of the risk of surgery has been eliminated at the outset. This is borne out by the fact that the two deaths in the operated group, one at 7 days and the other at 5 months, occurred in patients with poor left ventricular function. Furthermore, it has been our policy to select patients in whom the

infarction is small or caused relatively little functional impairment or both. Such patients would be expected to have a better prognosis whether or not they were operated on early, and this assumption is supported by the results in the matched pair series.

We found no significant difference in survival between patients with or without post-infarction angina (Table 4), nor was there a significant difference in survival between those operated on and the matched non-operated patients. It is doubtful whether operation would materially affect one year survival in any event since it was carried out too late to influence the primary infarct size itself.¹¹ DeWood *et al*¹ and Berg *et al*⁴ have reported that operation at a sufficiently early stage of infarction may limit infarct size and improve survival, although this can not be taken as proven since their patients formed a consecutive series without concurrent controls. The major benefit of surgery in our

Table 4 Comparison of patients without and with post-infarction angina who survived the first 72 hours after myocardial infarction (472 patients)

Variable	No post-MI angina	Post-MI angina	p
No of cases	374	98	—
Age (years)	57 (12)	60 (10)	NS
Males	301 (80%)	75 (77%)	NS
Length of stay (days)	12.9 (8.8)	18.8 (10.7)	0.001
Ejection fraction	0.45 (0.16)	0.46 (0.13)	NS
	(303 cases)	(86 cases)	
History of old MI	114 (30%)	36 (37%)	NS
History of AP for more than 4 weeks	110 (29%)	61 (62%)	0.001
Location of MI			NS
Transmural anterior	144 (38%)	31 (32%)	
Transmural inferior	139 (37%)	34 (35%)	
Non-transmural	85 (23%)	32 (33%)	
Unknown/undefinable	6	1	
Peak serum CK (IU/l)	620 (540)	520 (420)	NS
Killip clinical class			NS
I	237 (63%)	64 (65%)	
II	90 (24%)	24 (24%)	
III	23 (6%)	6 (6%)	
IV	24 (6%)	4 (4%)	
Wedge pressure (mm Hg)	12.9 (6.5)	11.3 (6.0)	NS
Cardiac index (l/min/m ²)	2.8 (0.8)	2.6 (0.8)	NS
Mean arterial pressure (mm Hg)	123 (22)	123 (20)	NS
Death in hospital	27 (7%)	5 (5%)	NS
Death after discharge			
within one year	39 (10%)	13 (13%)	NS
Non-fatal reinfarction	43 (11%)	12 (12%)	NS
Total one year survival	317 (85%)	83 (85%)	NS
Medication at discharge:			
Anticoagulants	74 (20%)	19 (19%)	NS
Beta blockers	147 (39%)	63 (64%)	0.001
Digoxin	88 (24%)	18 (18%)	NS
Diuretics	129 (34%)	37 (38%)	NS
Nitrates	91 (24%)	73 (74%)	0.001
Calcium antagonists	46 (12%)	60 (61%)	0.001
Antiarrhythmics	18 (5%)	4 (4%)	NS

Data reported as events and percentage of cases or as mean (SD). All percentages computed over entire series of 374 and 98 cases respectively. NS, difference not significant at the 0.05 level. MI, myocardial infarction; AP, angina pectoris; CK, creatine kinase.

series thus is the effective management of refractory post-infarction angina. Nevertheless, the decision to perform bypass grafting for this indication soon after infarction remains a matter requiring careful judgment in each patient.

These data were gathered during a period when percutaneous transluminal coronary angioplasty started to gain acceptance at our institution. It is clear that angioplasty is having an impact on our policy to refer patients for operation; more patients receive angioplasty first, and those with unsatisfactory results or complications are later referred for operation.¹² Meyer *et al* have reported that angioplasty can be carried out at low risk and with good early and late results in patients with unstable angina pectoris.¹³ But results from randomised trials designed to evaluate the long term success rate of this policy have not yet appeared. Also it remains to be seen what effect the widespread availability of thrombolytic agents such as recombinant tissue type plasminogen activator¹⁴ will have on the management of these patients.

In summary, the results presented here for coronary artery bypass surgery after acute myocardial infarction show that this procedure can be carried out with low operative mortality and one year mortality. In patients with post-infarction angina in whom an extension of infarction is threatened operation should be considered provided that the infarct is small and that left ventricular function is good. We must emphasise, however, that if angina can be controlled by medical treatment early after infarction, then this remains the preferred approach. The most striking difference between the operated and non-operated matched pairs is the recurrence of angina within one year that required aggressive medical treatment, angioplasty, or coronary bypass graft surgery.

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Myocardial infarct size and mortality in diabetic patients

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SUMMARY The mortality rate from myocardial infarction is disproportionately high in diabetic patients. One explanation for this may be that diabetic patients incur more extensive myocardial necrosis. This possibility was examined in a three part study. Firstly, peak serum aspartate aminotransferase concentrations of all diabetic and non-diabetic patients admitted with myocardial infarction over a 16 year period were compared retrospectively. Secondly, peak aspartate aminotransferase concentrations in a series of diabetic patients and controls matched by age and sex were examined retrospectively. Thirdly, creatine kinase MB release and electrocardiographic measures of infarct size were investigated prospectively in a case/control study. Although cardiac failure and death were more common in the diabetic groups, there were no significant differences in estimates of infarct size between diabetic and non-diabetic patients in any of the studies.

Therefore, the high case fatality rate amongst diabetic patients is not caused by increased myocardial damage. Presumably survival is prejudiced by factors operating before the infarction.

Diabetic patients are at increased risk of death from myocardial infarction.^{1,2} Not only is there a higher incidence of infarction³ but the case fatality rate is about 1.5 to 2.0 times higher than it is in non-diabetic patients.^{4,5}

In general, the major determinant of mortality once the patient has reached hospital is the degree of myocardial necrosis,^{6,7} and, therefore, one explanation of the diabetic death rate could be more extensive infarction. There are theoretical reasons why this might be so—diabetic patients may have more extensive coronary disease⁸; local tissue oxygenation may be disproportionately impaired by a combination of basement membrane thickening,⁹ decreased deformability of red cells,¹⁰ increased viscosity,¹¹ and hypercoagulability of blood¹²; also a relative insufficiency of insulin¹³ is likely to lead to impairment of glycolysis (the only source of high energy phosphate in ischaemia¹⁴) and to an undue increase in non-esterified fatty acids which may further increase infarct size.¹⁵

Therefore, in trying to unravel the cause of the high mortality from myocardial infarction in diabetic patients it is important to determine whether

infarct size is greater in these patients. We have evaluated infarct size in three separate surveys in an attempt to explore the possible causes of increased mortality from myocardial infarction in diabetic patients.

Patients and methods

We conducted three separate surveys.

SURVEY 1967-83

All patients known before admission to be diabetic who were admitted to the coronary care unit between January 1967 and December 1983 with myocardial infarction were studied retrospectively. Myocardial infarction was diagnosed by the presence of two out of three of the following criteria: ischaemic pain lasting more than 30 minutes; development of new Q waves of longer than 30 ms duration; and a rise in serum aspartate aminotransferase concentrations to greater than twice the upper limit of normal.

For convenience only half of the non-diabetic patients were evaluated. Four periods of two years (1967-68, 1972-73, 1977-78, and August 1981 to December 1983) were selected and all non-diabetic patients admitted to the coronary care unit with myocardial infarction during these years were identified. Patients in whom diabetes was diagnosed

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Accepted for publication 12 July 1985

only after admission were excluded from the study and patients who were re-admitted were treated statistically as a second patient. Peak serum aspartate aminotransferase and hospital mortality were determined from hospital records. The assay for aspartate aminotransferase has not altered over the past 16 years.

SURVEY 1979-83

In a second retrospective study all diabetic patients admitted from January 1979 to December 1983 with myocardial infarction were matched by age (± 5 years) and sex with the next appropriate non-diabetic patient who was admitted. For these patients peak aspartate aminotransferase, hospital course, and mortality were determined. To be sure that peak aspartate aminotransferase concentration had been measured we excluded patients admitted more than 48 hours after the onset of pain and those who died less than 24 hours after the onset of pain.

SURVEY 1982-84

In a prospective study, all diabetic patients admitted from July 1982 to May 1984 suspected of having a myocardial infarction were paired with the next non-diabetic patient, matched by age (± 5 years), sex, and presence or absence of a previous history of myocardial infarction (irrespective of the number of infarcts). Patients were excluded if the onset of pain occurred more than 12 hours before admission to the coronary care unit. Blood was sampled on admission and every eight hours for 72 hours. All patients suspected of having an infarction were studied, but patients were later excluded if they did not meet the diagnostic criteria. Results from those who died within 72 hours (before the blood sampling was completed) were also excluded.

All patients had electrocardiographic monitoring for 24 hours with access to immediate write-out. We noted arrhythmias that were unlikely to be overlooked: complete heart block, ventricular fibrillation and atrial fibrillation. Left ventricular failure (diagnosed on the basis of the following—a third heart sound, widespread crepitations, or a chest x ray film showing pulmonary oedema) and cardiogenic shock (hypotension, poor perfusion, and low urine output) were also noted.

Analysis of creatine kinase MB

Plasma concentrations of creatine kinase MB isoenzyme activity were determined by an immunoinhibition method (kit no 300691; Boehringer Mannheim) at 340 nm and expressed as U/l at 37°C. Plasma specimens treated with edetic acid were used and a plasma blank correction was determined and applied to each specimen.

Calculation of infarct size

The mean plasma concentration of creatine kinase MB in a series of 30 hospital patients without myocardial infarction was 20 U/l and this was subtracted from all values of creatine kinase MB. The disappearance coefficient (kd) was calculated by application of exponential regression analysis to the descending portions of the creatine kinase MB time curve (using a Super-Brain Computer and Stats-pak programme). The infarct size was calculated by the formulas of Shell *et al.*¹⁶ as modified by Norris *et al.*¹⁷ For small infarcts, where there is a degree of inaccuracy in the determination of kd, we made the arbitrary rule that if the correlation coefficient of the regression line was less than 0.95 that value of kd was rejected and the mean of the pooled values of kd was used.

Comparison of creatine kinase MB kinetics

We analysed the release of creatine kinase MB in the diabetic and non-diabetic patients by comparing the disappearance coefficient and the time to peak creatine kinase MB in the two groups. In addition, the creatine kinase MB released was found for each patient at 6, 12, 18, and 24 hours by extrapolation of each curve and this was then expressed as a percentage of total creatine kinase MB released, these percentage values were averaged for the two groups so that accumulation curves for diabetic or non-diabetic patients could be compared.

Electrocardiographic analysis

To support the enzyme data we also used two simple electrocardiographic analyses of infarct size—QRS scoring¹⁸ and the presence or absence of reciprocal ST depression.¹⁹ For the QRS score the 12 lead electrocardiogram was recorded daily at a standard speed (25 mm/s) and sensitivity (1 mV/cm); the last available electrocardiogram up to and including the seventh day after infarction was analysed for this purpose. Patients with previous infarction, left ventricular hypertrophy, or conduction abnormalities were excluded from the QRS scoring study. Reciprocal depression was defined as ST depression of 1 mm or more in at least two leads remote from the infarct site and was scored as being present if seen on any electrocardiogram. Patients with electrocardiographic defects were also excluded from this study.

Study size

From our initial study of aspartate aminotransferase and mortality in non-diabetic patients, it was evident that if the excess mortality in our hospital were solely the result of increased infarct size, then the diabetic population would be expected to have 50% more myocardial necrosis than the non-diabetic pa-

tients. Using this figure, a power of 90%, the standard deviation of a pilot study on creatine kinase MB sizing of infarcts, and looking for significance at the 5% level we calculated that data from 25 matched pairs were needed to exclude a positive result²⁰ (in the end we recruited 38 pairs).

STATISTICS

Groups were compared by Student's *t* tests and by χ^2 tests with the Yates's correction as appropriate.

Results

RETROSPECTIVE STUDY 1967-83

From 1967 to 1983, the 456 diabetic patients admitted with myocardial infarction had a hospital mortality of 33.6%, in contrast to the 18.3% mortality ($p < 0.001$) in 1516 non-diabetic patients admitted over the four two year periods of the study. Serum aspartate aminotransferase levels and mortality data were available for 1516 (78%) of the non-diabetic patients and 328 (72%) of the diabetic group. The distributions of serum aspartate aminotransferase concentrations are almost identical in the two groups (Fig. 1). Mortality increased with peak aspartate aminotransferase in both groups (Fig. 2), but at any aspartate aminotransferase concentration mortality in the diabetics exceeded that in the non-diabetics ($p < 0.001$), suggesting that the excess mortality is not solely due to infarct size.

CASE MATCHED STUDY 1979-83

Over the period of this study 167 diabetic patients were admitted with infarction; 50 died (30%). During the same period 228 (18.6%, $p < 0.001$) of 1224 non-diabetic patients died. We studied 120 pairs of

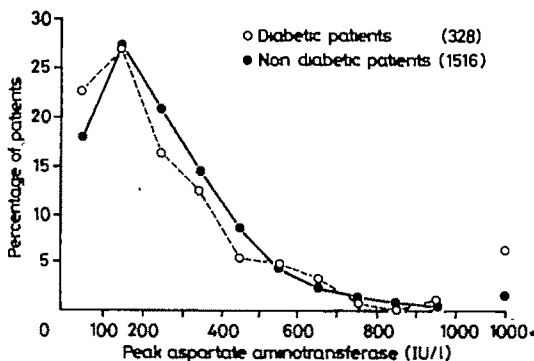


Fig. 1 Distribution of peak serum aspartate aminotransferase concentrations in retrospective analysis of 1967-83 data from diabetic and non-diabetic patients with myocardial infarction.

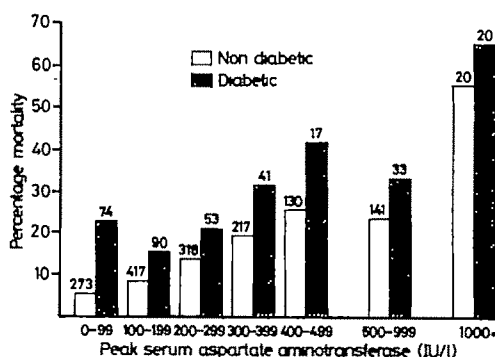


Fig. 2 Mortality of peak serum aspartate aminotransferase concentrations in 1967-83 retrospective analysis of diabetic and non-diabetic patients with myocardial infarction. Numbers above the bars are the number of patients.

patients from these groups; the two age and sex matched groups were similar (Table 1) for prevalence of hypertension, previous myocardial infarction, and renal dysfunction (as judged by admission creatinine concentrations). Arrhythmias were not more common in the diabetic group but haemodynamic problems (cardiogenic shock plus left ventricular failure) were (49% compared with 28% in the non-diabetics, $p < 0.01$), and Killip and Kimball grading was also significantly different in the two groups.²¹ In the diabetic group there was a statistically significant increase in the frequency of cardiogenic shock and an increase (but not a significant one) in left ventricular failure. To test for bias in our clinical haemodynamic assessment we looked at the death rate for each heart disease category. For cardiac failure, 27% of the diabetic and 23% of the non-diabetic patients died and for cardiogenic shock 94% of diabetic and 100% of non-diabetics died. These values are so similar that diagnostic bias seems unlikely. The death rate in the diabetic group was higher than that in the non-diabetic group (23% vs 9%, $p < 0.01$); the overall death rate was lower than that in the 1967-83 survey because of the exclusion criteria used. But despite the higher frequency of haemodynamic failure and death in the diabetics serum aspartate aminotransferase concentrations were almost identical in the two groups (mean diabetic concentration 366 U/l, mean non-diabetic 357 U/l, Fig. 3). This accords with the conclusions of the previous study that excess mortality in diabetic patients is not simply due to infarct size.

PROSPECTIVE CREATINE KINASE MB CASE CONTROL STUDY (1982-84)

Sixty five diabetics were admitted to hospital in this study period and 24 were excluded (10 died before

Table 1 Survey 1979-83

Patients	Diabetic	Non-diabetic	Significance
No	120	120	
Age in years	62.4 (9.2)	62.2 (9.0)	NS
Sex	91 male	91 male	NS
Previous history			
Hypertension	15 (13%)	19 (16%)	NS
Myocardial infarction	27 (23%)	15 (13%)	NS
Serum creatinine > 125 $\mu\text{mol/l}$	28 (25%)	18 (17%)	NS
Serum creatinine > 300 $\mu\text{mol/l}$	1 (1%)	2 (2%)	NS
Complications			
Atrial fibrillation	19 (16%)	18 (15%)	NS
Complete heart block	16 (13%)	8 (7%)	NS
Ventricular fibrillation	10 (8%)	14 (12%)	NS
Left ventricular failure	41 (34%)	31 (26%)	NS
Cardiogenic shock	18 (15%)	3 (3%)	$p < 0.01$
Left ventricular failure and shock	59 (49%)	34 (28%)	$p < 0.01$
Killip grades			
1	75	98	$p < 0.001$
2	23	19	
3	10	2	
4	12	1	
Death	28 (23)	11 (9)	$p < 0.01$
Enzymes			
Serum aspartate aminotransferase (U/l)	366 (322)	357 (236)	NS

Figures are means (1 SD) and percentages. Serum creatinine was measured at admission in only 110 diabetics and 106 non-diabetic patients.

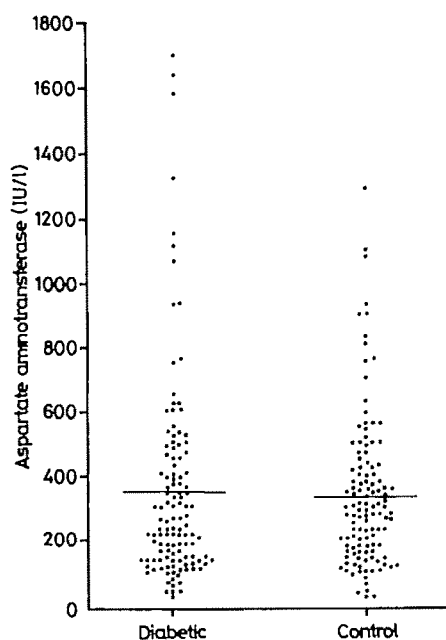


Fig. 3 Distribution of peak serum aspartate aminotransferase concentrations in 1979-83 survey of diabetic and non-diabetic patients with myocardial infarction. Horizontal lines indicate mean values.

completion of enzyme sampling, 11 arrived 12 hours or more after the onset of pain, and three were excluded at the request of their own physician). Of the 41 remaining patients two could not be matched by the end of the study and one had a reinfarction 24 hours after admission. These patients were not included.

The 38 study patients (Table 2) had been diagnosed as diabetic a mean of 11.2 years ago; seven were being treated by diet, 20 with oral agents, and 11 with insulin; five had some degree of retinopathy, three had proteinuria, and three had peripheral vascular disease. The histories of diabetic and non-diabetic patients were similar but fewer diabetic patients were current smokers. The frequency of arrhythmias was similar in the two groups. There was a trend to more haemodynamic complications but the numbers are too small for valid statistical analysis. Because of the exclusion criteria the death rate was low in both groups.

Whatever the method of assessment used diabetic patients did not have larger infarcts than non-diabetic patients (Table 3). The 95% confidence limits of the sum of creatine kinase MB release are such that infarct size in diabetic patients might have exceeded by up to 33 U/l that in non-diabetics, but the chance that a larger excess could have been missed is less than 2.5%. If the non-diabetic sample is assumed to be identical with the non-diabetic population, the maximum excess diabetic infarct size that could be missed by chance (at the 2.5% level) would be 6% of the infarct size in



Table 2 Survey 1982-84

<i>Patients</i>	<i>Diabetic</i>	<i>Non-diabetic</i>	<i>Significance</i>
No	38	38	
Age in years	60.7 (9.4)	60.7 (9.0)	NS
Sex	27 male	27 male	NS
<i>Previous history</i>			
Hypertension	11 (29%)	13 (34%)	NS
Myocardial infarction	10 (26%)	10 (26%)	NS
Angina	4 (11%)	5 (13%)	NS
Current smoker	9 (24%)	21 (55%)	p < 0.01
<i>Electrocardiogram abnormality</i>			
Anterior infarct	17	15	NS
Inferior infarct	19	22	
Right bundle branch block	1	1	
Left bundle branch block	1	0	
<i>Complications</i>			
Atrial fibrillation	6 (16%)	5 (13%)	NS
Complete heart block	3 (8%)	4 (11%)	NS
Ventricular fibrillation	3 (8%)	4 (11%)	NS
Left ventricular failure	17 (45%)	10 (26%)	NS
Cardiogenic shock	3 (8%)	2 (5%)	NS
Left ventricular failure and shock	20 (53%)	12 (32%)	NS
<i>Kilohp</i>			
1	31	33	NS
2	5	4	
3	2	0	
4	0	1	
<i>Death</i>			
	3	2	NS

Figures are means (1 SD) and percentages.

Table 3 Estimation of infarct size

	<i>Diabetic</i>	<i>Non-diabetic</i>	<i>Significance</i>
<i>By enzyme</i>			
Peak aspartate aminotransferase (U/l)	472 (402)	421 (321)	NS
Peak creatine kinase MB (U/l)	240 (129)	297 (174)	NS
Sum of creatine kinase MB (U/l)	414 (241)	525 (382)	NS
Creatine kinase MB (gram equivalent)	24.0 (14.3)	31.7 (25.4)	NS
Creatine kinase MB (g/m ²)	13.3 (7.9)	17.1 (13.1)	NS
<i>By electrocardiogram</i>			
Reciprocal depression	22 (61%)*	21 (57%)*†	NS
QRS Score	5.7 (3.2)‡	6.9 (3.5)‡	NS

*36 patients available for analysis. †37 patients available for analysis. ‡23 patients available for analysis. NS, not significant. Figures are means (1 SD) and percentages.

Table 4 Creatine kinase MB kinetics in diabetic and non-diabetic patients with myocardial infarction

	<i>Diabetic</i>	<i>Non-diabetic</i>	<i>Significance</i>
Disappearance coefficient (kd)	-0.071	-0.068	NS
Time to peak creatine kinase MB (h)	20.7	22.8	NS
<i>Percentage of total creatine kinase MB released by</i>			
6 h	13	10	NS
12 h	40	41	NS
18 h	68	71	NS
24 h	85	90	NS

NS, not significant.

non-diabetic patients. The creatine kinase MB kinetics of diabetic and non-diabetic patients were compared (Table 4). The coefficient of disappearance (kd), time to peak creatine kinase MB concentration, and the rate of release of creatine

kinase MB expressed as a percentage of total creatine kinase MB release were identical in the diabetic and non-diabetic groups.

The 12 lead electrocardiographic data were examined for the two semiquantitative indices of

infarct size—reciprocal ST depression and QRS score—and results in the diabetic and non-diabetic patients were almost identical. Therefore, it is very unlikely that diabetic patients have bigger infarcts than non-diabetic patients.

Hyaluronidase

For some years this hospital has been assessing the effect of treatment with hyaluronidase (GL enzyme) on myocardial infarction.²² Twenty three per cent of patients in the 1979–83 survey and 20% of those in the 1982–84 survey were given the drug. This is unlikely, however, to have altered our conclusions because in our experience²² and that of others²³ hyaluronidase does not reduce infarct size in man as judged by cardiac enzyme release (aspartate aminotransferase or creatine kinase MB). Also it could not alter the significance of the observation that there is disparity between enzyme concentrations and mortality in the two groups; and, finally, the results are unchanged by exclusion from the analysis of all patients receiving hyaluronidase.

Discussion

The frequency of diabetes among all patients studied may have been underestimated because many were seen before haemoglobin A₁ estimation had become common practice.²⁴ Even so, approximately 2% of the apparently non-diabetic population was found to be diabetic on admission to hospital and these patients have been excluded from the study. The remainder of the non-diabetic population may have contained a further 2–3% of diabetic patients²⁵ who could now be detected by measurement of haemoglobin A₁ but this is too small a figure significantly to influence the results.

To our knowledge no one has examined the validity of creatine kinase MB kinetics as an estimate of infarct size in the diabetic patient. This requires a parallel necropsy study which we did not perform, nor were sufficient patients available for such a study. But the disappearance coefficients, the time to peak creatine kinase MB concentrations, and the rates of accumulation of creatine kinase MB are all so similar in the two groups (Table 4) that it seems very unlikely that creatine kinase MB kinetics differ in diabetic patients.

Among those diabetic patients reaching hospital, the majority of deaths (80–85%) are due to pump failure.²⁶ In this respect they are no different from non-diabetic patients (and this study shows that arrhythmias are not more prevalent in diabetics and previous work from this hospital also indicates that ketoacidosis is a rare (3%) complication of infarction in diabetic patients²⁷). An alternative explanation of

the high mortality in diabetic patients could be that they have a greater degree of myocardial necrosis which in turn might be due to more extensive coronary atheroma in diabetes; poor tissue oxygenation due to abnormalities of the micro-circulation^{9–12}; or the pronounced impairment of glycolysis¹⁴ and raised non-esterified fatty acid concentrations¹⁵ that would be expected in the diabetic patient after infarction.

We have examined the possibility of a systematic increase in infarct size in diabetics by using three complementary sets of observations—a retrospective 16 year study of all diabetics with a relatively non-specific enzyme method of estimating infarct size, a matched series in which aspartate aminotransferase was measured, and a study which excluded some of the more seriously ill patients but which used a more specific and precise enzyme technique (creatin kinase MB) reinforced by analysis of the 12 lead electrocardiogram. In none of these three sets of patients did the diabetic patients have larger infarcts than the non-diabetic ones. This accords with the results of Jaffe *et al* who showed that although diabetic patients have increased rates of cardiac failure after myocardial infarction, infarct size in these patients is less than that of the non-diabetic patients.²⁸

Thus, although in theory there are mechanisms by which the diabetic might be at risk of more extensive infarction, these do not appear to be important in practice. We have also found that careful metabolic control after infarction has little effect on mortality.²⁹ Therefore, the unknown cause of the excess death rate may well operate before the fatal infarction occurs. The most likely explanation appears to be previous left ventricular disease, possibly vascular in origin or possibly related to some other aspect of diabetes. Attempts to improve survival among diabetic patients should be instituted before the onset of infarction.

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Classification of non-Q-wave myocardial infarction according to electrocardiographic changes

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SUMMARY The characteristics of 93 patients in whom electrocardiographic recordings were obtained within 12 hours of the onset of non-Q-wave myocardial infarction were studied. Patients were divided into the three groups according to what electrocardiographic changes were seen. Forty nine patients had ST segment depression, 35 had ST segment elevation, and nine had T wave changes. Patients with ST segment depression had a higher rate of pump failure and multi-vessel disease than the other two groups. There were no significant differences in peak serum creatine kinase activity among the three groups. Twelve of 13 patients who died of non-Q-wave myocardial infarction in hospital had ST segment depression. Furthermore nine of them had attacks of non-Q-wave myocardial infarction with severe ST segment depression in many leads. At necropsy five of six patients who had shown severe ST segment depressions in many leads at the onset of non-Q-wave myocardial infarction were found to have circumferential sub-endocardial lesions with triple vessel disease.

This study suggests there are electrocardiographic subtypes of non-Q-wave myocardial infarction that are associated with specific patient characteristics.

Acute myocardial infarction has been divided into transmural myocardial infarction and non-transmural myocardial infarction on the basis of the development of abnormal Q waves. Several previous studies comparing the characteristics of patients with non-transmural myocardial infarction and transmural myocardial infarction have reported conflicting results. Although some studies reported a lower hospital mortality in patients with non-transmural myocardial infarction than in those with transmural infarction,^{1,2} in others no significant differences were seen between the two groups.³⁻⁵ This may be because several clinical subtypes are included in the category non-transmural myocardial infarction. Few attempts have been made to identify these subtypes.⁶⁻⁸ Equally important is the inability to distinguish between non-transmural and transmural myocardial infarctions on the basis of abnormal Q waves alone.⁹ It is more accurate to use the terms Q wave infarctions and non-Q-wave infarctions.⁹

We have investigated the characteristics of subtypes of non-Q-wave myocardial infarction. These subtypes were classified into three groups according to the electrocardiographic changes seen at the onset of infarction.

Patients and methods

Patients—Four hundred and seventy seven consecutive patients were admitted to the coronary care unit at the National Cardiovascular Centre Hospital between October 1977 and June 1982 with suspected acute myocardial infarction. Those who fulfilled the three criteria for diagnosis of non-Q-wave myocardial infarction and from whom electrocardiograms had been obtained within 12 hours of the onset of acute myocardial infarction were included in this study. The criteria for diagnosis were (a) chest pain compatible with acute myocardial infarction, (b) peak serum creatine kinase activity which was at least twice the upper limit of normal, and (c) persistent ST segment changes, persistent T wave changes, and absence of new abnormal Q waves (that is Q waves lasting more than 0.04 seconds and with an amplitude which was more than 25% of the subsequent R waves). In addition to cri-

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Accepted for publication 16 July 1985

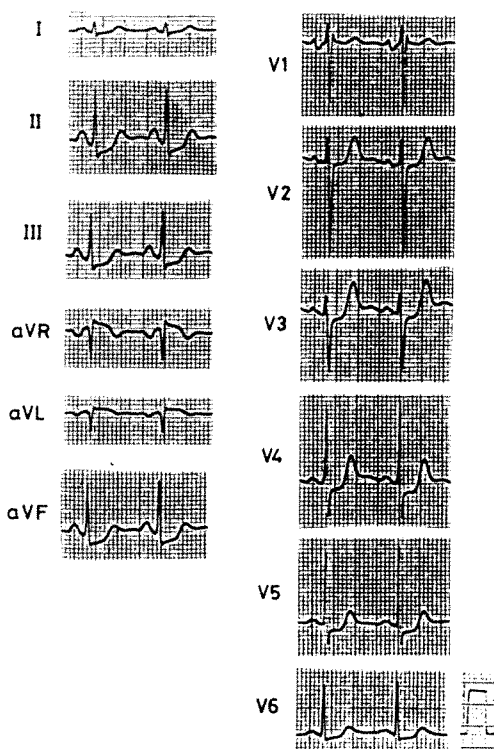


Fig. 1 Electrocardiogram in a 71 year old man showing ST depression in leads II, III, aVF, and V3-V6. This patient was in Killip class I and peak serum creatine kinase activity was 1356 IU/l.

teria (a) and (b) the diagnosis of Q wave myocardial infarction required the development of abnormal Q waves. In the case of posterior infarction, the development of initial R waves in leads V1 and V2 of 0.04 seconds' duration with a R/S ratio greater than 1 is considered to be as important as the development of an abnormal Q wave. Ninety three patients with non-Q-wave myocardial infarction fulfilled all these criteria.

Electrocardiogram and serum creatine kinase activity were measured every three hours from the onset of infarction for 24 hours and every six hours from the onset of infarction for the next two days. There were three types of electrocardiographic findings associated with non-Q-wave myocardial infarction: (a) onset with ST segment depression (Fig. 1); (b) onset with ST segment elevation (Fig. 2), and (c) onset with T wave changes and without important ST segment changes (Fig. 3). We defined a finding of ST segment elevation in some leads and ST segment depression in other leads as ST elevation.

Cardiac catheterisation—As a rule hospital sur-

vivors aged ≤ 65 years with non-Q-wave myocardial infarction had coronary angiography about 4 weeks after the acute event. In some cases coronary angiography was also performed at necropsy. Coronary stenosis was regarded as important when a reduction of more than 75% of the luminal diameter was demonstrated in a major artery.

Statistical analysis—The results were analysed by the χ^2 test and Student's *t* test.

Results

Of the 93 patients with non-Q-wave myocardial infarction in whom electrocardiographic recordings were obtained within 12 hours of onset, 49 had ST depression, 35 had ST elevation, and nine had T wave changes (Fig. 4a).

The average (SD) age of patients was similar in these three groups (ST depression 63.4 (10.2), ST elevation 58.9 (9.1), T wave changes 63.8 (9.1). Men comprised 76% of patients with ST depression, 80% of those with ST elevation, and 78% of those with T wave changes.

The patients were classified by Killip grade.¹⁰ Of those with ST depression, 28 (57%) were in Killip class I, 11 in class II, four in class III, and six in class IV. Of those patients with ST elevation, 30 (86%) were in class I, two in class II, two in class III, and one in class IV. All nine patients with T changes were in Killip class I. Thus, pump failure was significantly more common in patients with ST depression than those with the other two types of electrocardiographic change ($p < 0.01$) (Fig. 4b).

Angiographic findings—Coronary angiography (including nine post mortem angiograms) was performed in 51 patients. The results were classified into four groups: patients without significant stenosis (group A), single vessel disease (group B), double vessel disease (group C), and triple vessel disease (group D). (Left main coronary artery disease was defined as double vessel disease.) Of the patients with ST depression, one was in group A, one in group B, three in group C, and 20 in group D. In contrast, of the patients with ST elevation, one was in group A, six in group B, eight in group C, and seven in group D. In those with T changes, two were in group B and two in group C. Thus, multivessel (double or triple vessel) disease was significantly more common in patients with ST depression than in those with ST elevation or T wave changes (92% vs 68% and 50% respectively, $p < 0.05$). There was triple vessel disease in 80% of the patients with ST depression (Fig. 4c).

Peak serum creatine kinase activity was measured in 81 patients. Forty patients had ST depression, 33 patients had ST elevation, and eight patients had T

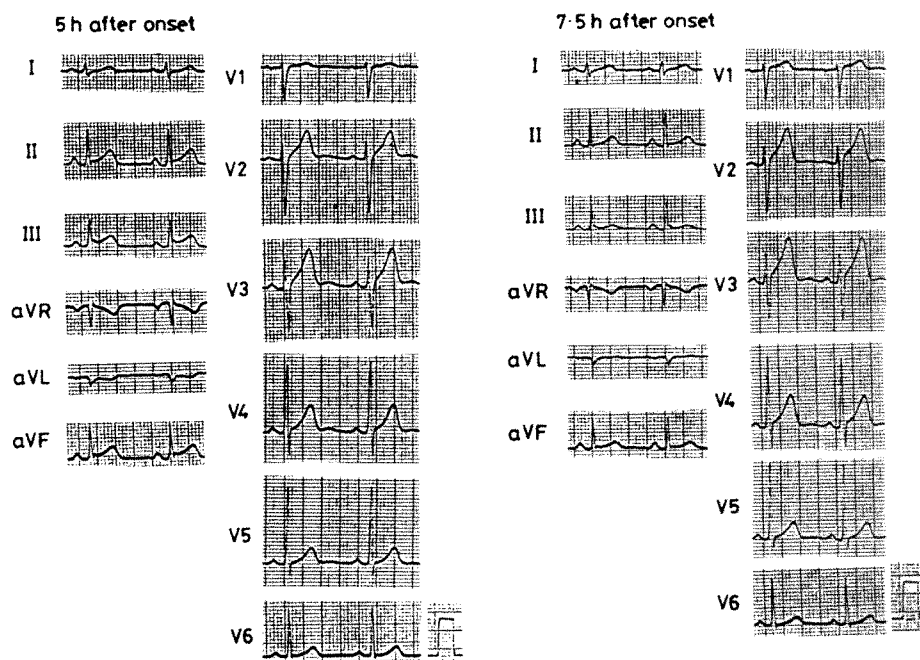


Fig. 2 Electrocardiogram in a man of 47 showing ST elevation in leads II, III, and aVF 5 hours after the onset of infarction. ST elevation resolved 7.5 hours after the onset of myocardial infarction. This patient was in Killip class I and had peak serum creatine kinase activity of 740 IU/l.

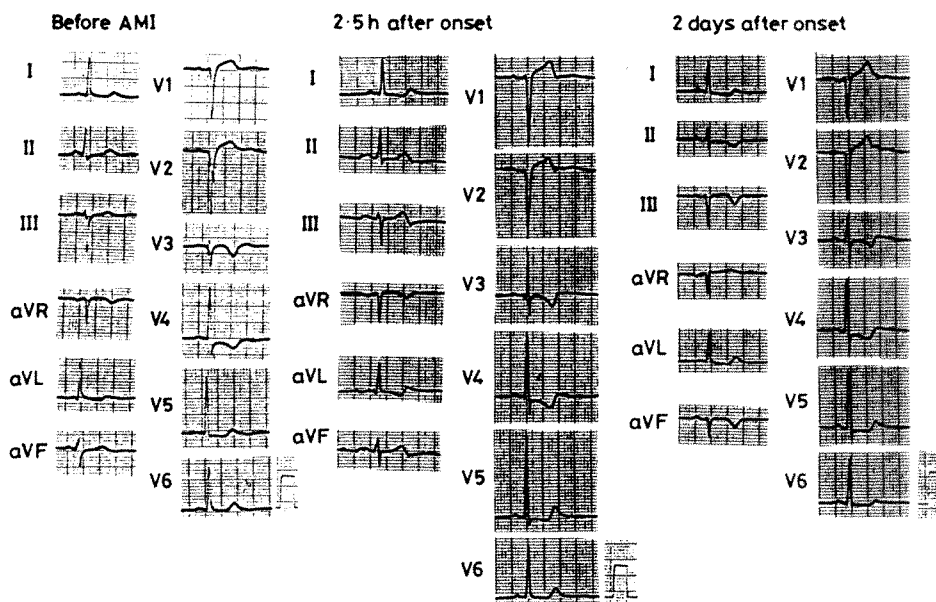


Fig. 3 Electrocardiogram in a man of 61 showing T wave changes in lead III 2.5 hours after the onset of myocardial infarction. A negative T wave later appeared in leads II, III, and aVF. This patient was in Killip class I and had peak serum creatine kinase activity of 500 IU/l.

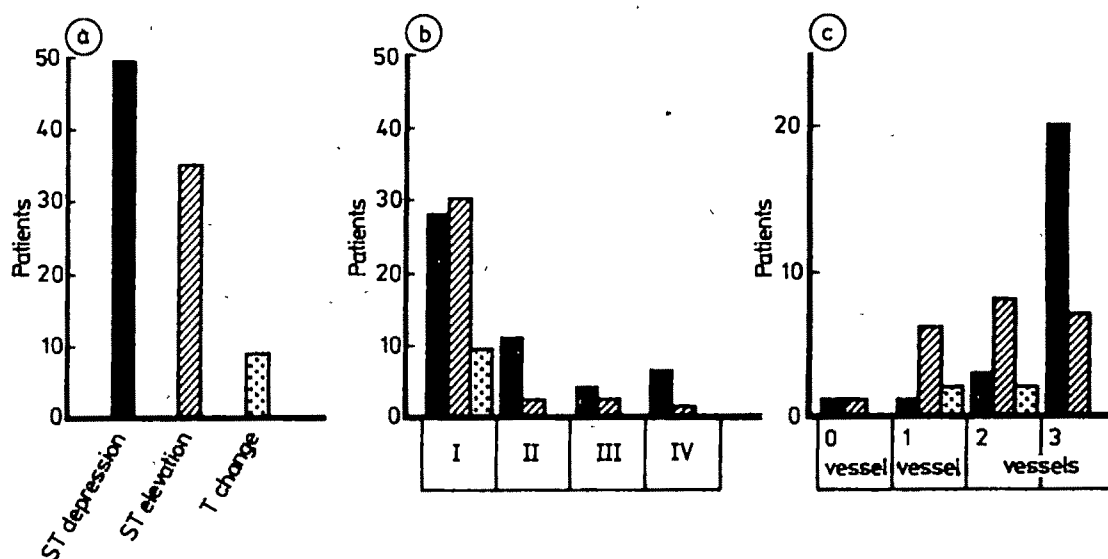


Fig. 4 Classification of non-Q-wave myocardial infarction by (a) electrocardiographic changes at onset, (b) Killip classification, and (c) number of significantly stenosed vessels ($\geq 75\%$ stenosis) in patients with the three types of electrocardiographic abnormality found in non-Q-wave myocardial infarction.

wave changes. Mean (SD) peak creatine kinase activity was 1420 (1197) IU/l in patients with ST depression, 1317 (1134) IU/l in those with ST elevation, and 777 (265) IU/l in those with T wave changes. None of these differences was statistically significant (Table).

Death—Thirteen patients died of non-Q-wave myocardial infarction in hospital. The cause of death was left ventricular failure in 12 patients and arrhythmia in one. Twelve patients had ST depression and one had ST elevation. No patient with T wave changes died. Thus, death while in hospital was significantly more common in patients with ST depression than in patients with ST elevation or T wave changes (24% *vs* 3% and 0% respectively, $p < 0.01$) (Table). Furthermore nine of the 12 patients with ST depression who died had pronounced and extensive ST segment depression at the onset of non-Q-wave myocardial infarction (that is ST segment depression ≥ 0.2 mV in at least one lead and definite ST segment depression in more than five of

the standard 12 leads). Necropsy in six of these nine patients showed that five of them had large sub-endocardial infarctions which were circumferential or nearly circumferential in extent. Angiography was performed post mortem on four of these five cases, and all four cases had triple vessel disease.

Discussion

The terms transmural myocardial infarction and non-transmural myocardial infarction have been used for many years in the electrocardiographic classification of acute myocardial infarction and they continue to be used despite evidence that the correlation with pathological findings is poor.² Because acute myocardial infarction without abnormal Q waves may or may not be seen in association with transmural infarction at necropsy, we prefer to use the terms "Q wave myocardial infarction" and "non-Q-wave myocardial infarction".

The diagnosis of non-Q-wave myocardial in-

Table Peak serum activities of creatine kinase (mean (SD)) and deaths in three types of non-Q-wave myocardial infarction

	ST depression	ST elevation	T wave change	Significance
Cases	49	35	9	
Peak creatine kinase (IU/l)	1420 (1197) (n=40)	1317 (1134) (n=33)	777 (265) (n=8)	NS
Deaths	12 (24%)	1 (3%)	0 (0%)	$p < 0.01$

NS, not significant.

farction is generally based on a triad of features: chest pain compatible with acute myocardial infarction, an abnormal increase in peak serum activity of cardiac enzymes, and an abnormal electrocardiogram. We defined abnormal peak serum creatine kinase as being at least twice the upper limit of normal activity. Almost all our patients had increases in creatine kinase MB, aspartate aminotransferase, and lactate dehydrogenase activity. The diagnosis of Q wave myocardial infarction depends not only on the presence of the first two criteria but also on the development of abnormal Q waves.¹¹⁻¹³ Many believe that acute myocardial infarction without abnormal Q waves can be distinguished clinically from infarction in which Q waves are normal.²⁻⁴

The frequency of left ventricular failure in non-Q-wave myocardial infarction is generally believed to be less than that in Q wave myocardial infarction.^{5,12,14} This may be partly due to the size as well as the location of the infarction, since levels of serum enzyme activity are generally higher in patients with Q wave infarction than in those with non-Q-wave infarction.^{1,5,15} In some patients, however, non-Q-wave myocardial infarction is complicated by severe left ventricular failure or cardiogenic shock.^{1,3,5} There may be clinical subtypes of non-Q-wave myocardial infarction, but there have been few reports identifying such subtypes.^{3,6} We classified patients with non-Q-wave myocardial infarction into three groups according to the electrocardiographic changes seen at the onset of infarction. Left ventricular failure (43%) and multivessel (double or triple vessel) disease (92%), and hospital mortality (24%) were more frequent in those with ST depression than in those with ST elevation or T wave changes. Twelve of 13 patients who died had ST depression. Peak creatine kinase activity in the serum, which is said to be associated with infarct size,^{15,16} was not significantly different in the three electrocardiographic groups. This was thought to be because the ST depression groups included non-Q-wave myocardial infarctions of various sizes. We examined in more detail the electrocardiographic changes of patients who died. Nine of the 12 patients with ST depression who died had severe and extensive ST segment depression at the onset of non-Q-wave myocardial infarction—that is ST segment depression ≥ 0.2 mV in at least one lead and definite ST segment depression in more than 5 of the standard 12 leads. Necropsies done in six of these 9 patients showed that five of them had large subendocardial infarctions which were circumferential or nearly circumferential in extent.

It is difficult to explain the mechanism of ST seg-

ment elevation at the onset of non-Q-wave myocardial infarction. One cause of ST segment elevation is coronary artery spasm, which could have initiated acute myocardial infarction in these patients.¹⁷⁻¹⁹ T wave inversion often occurred when the ST depression or elevation of the acute phase had resolved. The shortest duration of ST elevation was 2 hours and that of ST depression was 4 hours.

Our classification of non-Q-wave myocardial infarction according to the electrocardiographic changes seen at the onset of infarction is a useful indicator of outcome in the acute phase.

We thank Professor Hirofumi Yasue, Kumamoto University School of Medicine, and Professor David H Spodick, University of Massachusetts Medical School, for their helpful criticisms of this paper.

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Reciprocal ST depression in acute myocardial infarction

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SUMMARY ST segment depression in leads remote from those showing ST elevation during acute myocardial infarction has been attributed to benign electrical phenomena, distant myocardial ischaemia, or extensive myocardial damage. Eighty four consecutive survivors under 55 years of age with a first transmural myocardial infarction were studied. All patients had exercise tests six weeks after infarction and coronary angiography a mean of three months after infarction. Thirty eight (75%) of the 51 inferior and 19 (58%) of the 33 anterior infarcts showed reciprocal ST depression of ≥ 1 mm during the acute phase. Ten (26%) of the 38 patients with inferior infarcts and reciprocal depression had ST depression in the same leads on exercise. There was concomitant disease of the left anterior descending artery in four (40%) of these 10 patients and in five (18%) of the 28 with inferior infarcts with reciprocal depression but without ST depression in the same leads on exercise. Five (26%) of the 19 patients with anterior infarcts with associated reciprocal depression and four of the 14 without reciprocal depression had important right coronary artery disease. In patients with inferior infarction important disease of the left anterior descending artery could not be predicted by ST depression in particular lead groups. Therefore reciprocal ST depression during acute myocardial infarction does not predict concomitant disease in the coronary artery supplying the reciprocal territory.

ST segment depression in leads remote from those showing ST segment elevation has been attributed to a wide variety of mechanisms. Some workers have suggested that this represents a benign electrical phenomenon.¹⁻³ Others have suggested that it is due to ischaemia in another region distant from the infarct⁴⁻⁶ or that it is simply a manifestation of a large infarct.^{7,8}

Jennings *et al* and Salcedo *et al* showed a correlation between anterior ST depression during acute inferior myocardial infarction and disease of the left anterior descending artery.^{6,9} Jennings *et al* also found ST depression in the same leads on exercise testing early after infarction, and this was interpreted as implying reversible ischaemia in the non-infarcted area. These studies, however, were of patients selected for angiography because of persistent symptoms or complications and they were probably biased towards the inclusion of patients

with extensive coronary artery disease. We have attempted to determine the relation, if any, between reciprocal ST segment depression in acute myocardial infarction and disease in the coronary artery supplying the reciprocal territory.

Patients and methods

This was a prospective study of 96 consecutive patients aged ≤ 55 years admitted to the coronary care unit of this hospital with a first transmural infarction. Six patients died in hospital and six more were excluded because of heart failure (two), unwillingness to participate (two), or additional severe non-cardiac disease (two). The remaining 84 patients (74 males, 10 females; mean age 46.5 years) had exercise tests six weeks after infarction, and coronary angiography a mean of three months after infarction (range 1-6 months). The diagnosis of acute myocardial infarction was based on a history of prolonged chest pain, development of Q waves, and a rise in the concentration of serum creatine kinase to at least twice that at baseline. Three 12 lead electrocardiograms (on admission and 24 hours and 48

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Accepted for publication 16 July 1985

Table 1 *Modified Bruce protocol used in study*

Stage	Duration (min)	Speed (miles per hour)	Incline (degrees)
0	3	1.2	0
1/2	3	1.7	5
1	3	1.7	10
2	3	2.5	12
3	3	3.4	14
4	3	4.2	16
5	3	5.0	18

1 mile per hour = 1.6 km per hour.

hours after the onset of the acute event) were recorded to identify reciprocal changes.

ELECTROCARDIOGRAMS

In inferior infarction ST depression in leads V1-V4, I, and aVL was regarded as reciprocal. Reciprocal depression in these leads was further classified as ST depression in (a) V1-V4 alone; (b) I or aVL alone; or (c) those who had reciprocal depression in a combination of leads I, aVL, and V1-V4. In anterior infarction ST depression in any of leads II, III, or aVF was considered to be reciprocal. Reciprocal depression was defined as ST depression of ≥ 1 mm measured at least 0.08 s after the J point of the QRS complex in leads remote from the infarction site.

EXERCISE TESTING

Six weeks after infarction all 84 patients had exercise tests that followed a modified Bruce protocol (Table 1). Exercise started at Bruce level 0 and was stopped

if the patient had severe symptoms, a drop in blood pressure of greater than 20 mm Hg, a run of three consecutive ventricular extrasystoles, or ST depression of ≥ 3 mm.

CORONARY ANGIOGRAPHY

All patients had coronary angiography a mean of three months (range 1-6 months) after the acute infarction. All angiograms were reviewed by RH and IP and important stenosis was defined as $\geq 70\%$ reduction in intraluminal diameter compared with the immediate proximal segment of normal coronary artery as measured in any cine projection. At least two orthogonal views of each coronary vessel were obtained. In anterior infarction the coronary artery supplying the reciprocal territory was the right coronary artery or a dominant circumflex artery and in inferior infarction the left anterior descending artery was regarded as supplying the reciprocal territory.

STATISTICS

The χ^2 test and Student's unpaired *t* test were used for statistical analysis.

Results

The site of infarction was inferior in 51 (61%) and anterior in 33 (39%) of patients.

INFERIOR INFARCTION

Reciprocal changes were seen on electrocardiograms from 38 (75%) of the 51 patients with inferior myo-

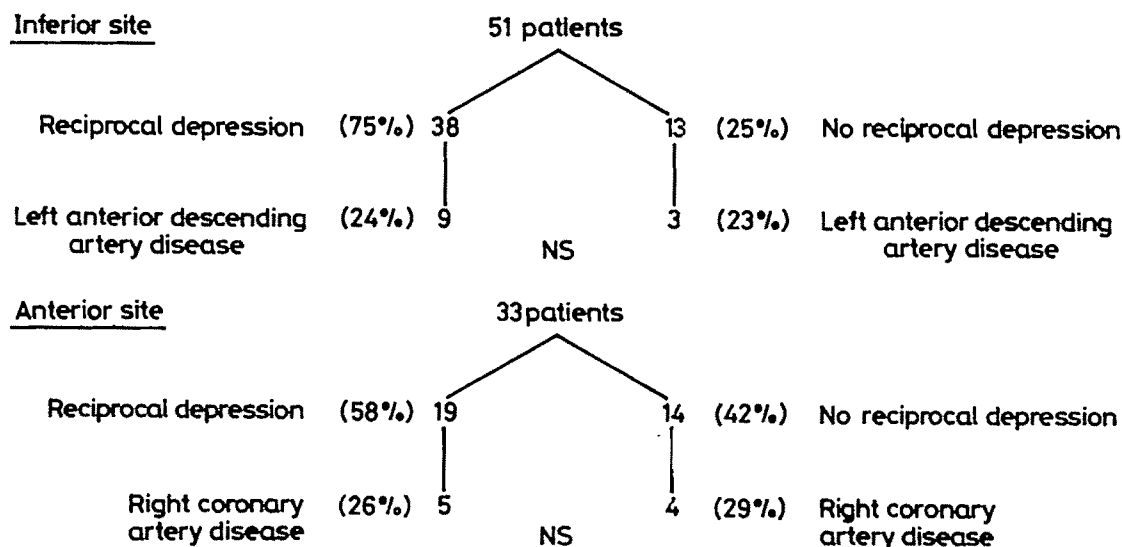


Fig. 1 Relation between reciprocal ST depression and important disease in artery supplying reciprocal territory.

Table 2 Relation between ST depression in different lead groups and disease in left anterior descending artery (LAD)

Lead	Patients	LAD disease	Predictive	Sensitivity	Specificity
V1-V4	4	0	0	0	88%
I, aVL	12	2	17%	22%	74%
I, aVL, and V1-V4	22	7	32%	78%	66%

cardial infarction (Fig. 1). Nine (24%) of the 38 patients showing reciprocal ST depression and three (23%) of the 13 patients without reciprocal depression had important disease of the left anterior descending artery. Therefore the presence of left anterior descending artery disease was not predicted by reciprocal ST changes. Ten (26%) of the 38 inferior infarct patients with reciprocal depression developed ST depression in the same leads on exercise (Fig. 2). Four (40%) of these patients had important disease of the left anterior descending artery. Thus 28 patients showing reciprocal depression did not have ST depression in the same leads on exercise. There was important disease of the left anterior descending artery in five (18%) of these 28 patients and four (40%) of the 10 patients who had ST depression in the same leads on exercise. This difference was not statistically significant.

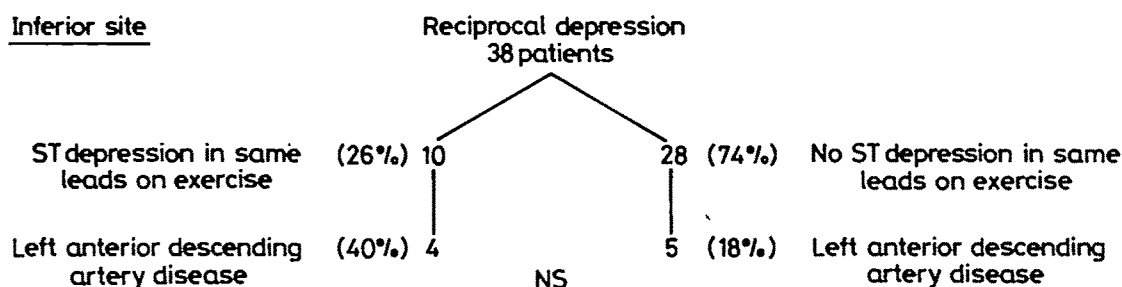
Table 2 shows the relation between ST segment depression in different lead groups and disease of the

left anterior descending artery. Only seven (27%) of 26 patients who showed ST depression in leads V1-V4 and nine (26%) out of 34 patients with ST depression in leads I and aVL, had important disease of the left anterior descending artery. Therefore important disease of the left anterior descending artery could not be predicted by ST depression in any particular grouping of leads.

ANTERIOR INFARCTION

Nineteen (58%) of the 33 patients with an anterior infarct showed reciprocal ST segment depression (Fig. 1). Five (26%) of these 19 and four (29%) of the 14 without reciprocal depression had severe right coronary artery disease. This difference was not statistically significant. Only one patient had ST depression in the same leads on exercise and this patient did not have severe right coronary artery disease (Fig. 2).

Inferior site



Anterior site

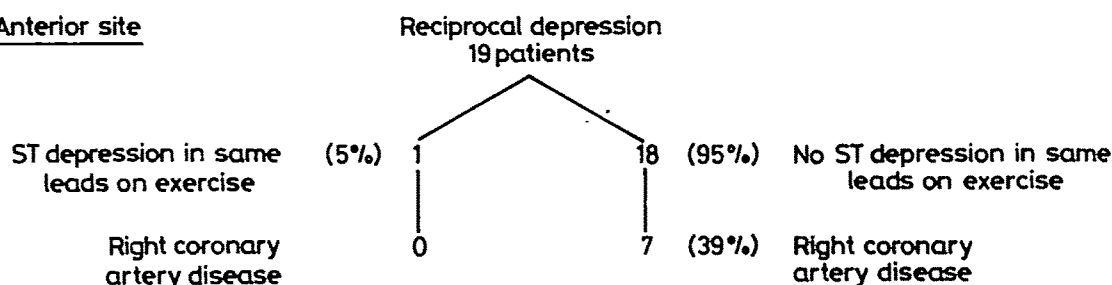


Fig. 2 Relation between acute reciprocal depression, ST depression in same leads on exercise, and coronary artery disease in reciprocal territory.

Table 3 Major complications occurring in hospital (complete atrioventricular block, left ventricular failure, supraventricular tachycardia, ventricular tachycardia)

	Patients	Complications
Reciprocal depression	57	13
No reciprocal depression	27	1
Total	84	14

COMPLICATIONS

Three of the six patients who died in hospital had reciprocal depression and five of the six patients with inferior infarction who developed severe complications in hospital had reciprocal depression (Table 3). These included complete atrioventricular block, persistent angina, and ventricular and supraventricular tachycardia. All eight patients with anterior infarction who went on to develop severe complications in hospital had reciprocal ST depression. Therefore 13 out of 14 patients who developed severe complications during admission had reciprocal ST depression compared with 44 out of 70 patients who did not.

Mean (SD) peak serum creatine kinase activity was 1900 (1350) units/l in patients with reciprocal depression and 1500 (1265) units/l in those without. This difference was not statistically significant.

SYMPTOMS

There was no significant difference between patients with and patients without reciprocal depression in the proportions who had angina at the time of coronary angiography.

Discussion

Reciprocal depression during acute myocardial infarction will have implications for management if patients with this feature constitute a high risk group in whom intervention to limit infarct size or alleviate distant ischaemia may favourably alter outcome. Wasserman *et al* found a correlation between the magnitude of inferior ST segment elevation and anterior ST segment depression in patients with inferior infarction.¹ In a follow up for an average of more than three years they did not find any difference in mortality between those with and those without reciprocal precordial ST segment depression. They concluded that reciprocal ST segment depression during the early phases of inferior infarction was an electrical reflection of primary ST segment elevation in the area of infarction. Billadello *et al* used positron tomography to show that 67% of

patients with reciprocal ST depression did not have anterior wall metabolic abnormalities during acute inferior infarction and they too concluded that reciprocal ST changes were electrical phenomena.¹⁰ They drew attention, however, to the finding that 33% of their patients had anterior wall metabolic abnormalities characteristic of ischaemia and suggested that in some cases reciprocal depression may represent distant ischaemia. Further support for this view came from Schuster and Bulkley in their review of 128 consecutive necropsies.⁴ They postulated that occlusion of one major coronary artery could interrupt collateral circulation and hence cause ischaemia in the distribution area of a second narrowed artery. Eight of their patients had angina after infarction and transient ST-T wave changes in the area supplied by a patent but critically narrowed vessel and they suggested that such patients may benefit from early aggressive intervention. Jennings *et al* and Salcedo *et al* lent further credence to this argument by showing a correlation between anterior segment ST depression during acute inferior myocardial infarction and disease of the left anterior descending artery.^{6,9} According to Salcedo *et al* reciprocal depression in leads V1-V4 was 95% predictive for disease in the left anterior descending artery.⁹ Jennings *et al* demonstrated ST depression in the reciprocal lead on exercise early after infarction in 63% of patients.⁶ They thought that this suggested important disease in the artery supplying this territory. In contrast in a large and detailed study Gibson *et al* showed that there was no significant difference either in the extent of underlying coronary artery disease or the frequency of left anterior descending artery disease between those with and those without reciprocal depression.⁷ Ferguson *et al* assessed angiographic results obtained during the acute phase of inferior infarction in six patients and also found that reciprocal depression did not predict the extent of coronary artery disease in the arteries supplying the remote wall.³

Only 10 out of 35 patients in the study of Jennings *et al* had coronary angiography.⁶ These 10 patients were catheterised because they had severe symptoms or complications. This could have biased the study towards patients with more extensive coronary artery disease. Our study consists of consecutive patients with acute anterior and inferior myocardial infarction who have had early routine postinfarction exercise tests and coronary angiograms without selection on the basis of symptoms. Our results accord with those of Gibson *et al*⁷ and Ferguson *et al*^{3,33} but not with those of Jennings *et al*⁶ and Salcedo *et al*.⁹ We found that neither reciprocal depression nor exercise induced ST segment depression in the same leads early after infarction predicted concomitant

disease in the coronary artery supplying the reciprocal territory. Unlike Salcedo *et al* we found that in acute inferior infarction reciprocal depression in specific lead groups V1-V4, I, and aVL does not predict concomitant disease in the left anterior descending artery.

Although several groups of workers,⁵⁻⁸ agree that reciprocal depression reflects more severe left ventricular damage, there are differences of opinions on what contribution remote wall damage makes to left ventricular dysfunction. Billadello *et al* found greater primary zone necrosis in those patients with reciprocal depression in acute inferior infarction than in those without reciprocal depression.¹⁰ Shah *et al*⁵ and Gibson *et al*⁷ used non-invasive tests to show that reciprocal ST depression in acute inferior infarction was associated with greater global and regional left ventricular dysfunction. Goldberg *et al* obtained similar results.⁸ Shah *et al* suggested that these findings may be a reflection of non-transmural infarction of the remote antero-septal wall,⁵ but Gibson *et al* believe that greater left ventricular dysfunction is simply a result of more extensive inferior or inferoposterior wall infarction and that antero-septal wall ischaemia need not be invoked.⁷ Goldberg *et al* showed a correlation between reciprocal ST segment depression in acute inferior infarction and the extent of posterolateral wall damage, but they did not rule out anterior wall ischaemia as an additional factor that may contribute to left ventricular dysfunction.

Our study was not specifically designed to study the relation between reciprocal depression and infarct size but the higher frequency of complications in our patients showing reciprocal depression accords with the results of Gelman and Saltups.¹¹ These findings suggest that patients with reciprocal depression have probably sustained larger infarcts.

Ian Peart was supported by the National Heart Research Fund and Catherine Albers by Bayer Pharmaceuticals.

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Characteristics of episodes of ST elevation or ST depression during ambulatory monitoring in patients subsequently undergoing coronary angiography

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SUMMARY Transient ischaemic ST segment changes were studied in 296 consecutive patients with coronary heart disease attending hospital for coronary arteriography. They underwent two channel, frequency modulated ambulatory monitoring for 24 hours. During this time 221 episodes of transient ST elevation ($n=56$) or ST depression ($n=165$) with a horizontal deviation of at least 1 mm lasting at least 1 min were found in 70 patients (23.6%). Only 34% of episodes were associated with pain. The duration of the episode, the heart rate at the beginning of the episode, or the extent of ST deviation were not related to the occurrence of pain. Episodes of ST elevation were of significantly shorter duration, occurred significantly more often during the early morning, and at significantly lower heart rates than episodes of ST depression.

The considerable overlap between the characteristics of episodes of ST elevation and ST depression suggests that in many instances a combination of factors is responsible for transient ischaemic ST segment changes.

The objective assessment of angina pectoris during daily life is based on the detection of ischaemic ST segment changes during continuous ambulatory electrocardiographic monitoring. The frequency of spontaneous ischaemic episodes has been investigated only in highly selected subgroups of patients¹⁻⁶ by means of amplitude modulated recording which is not reliable in the low frequency range.^{7,8} Frequency modulation overcomes these recording errors and fulfils the American Heart Association criteria for electrocardiographic recording.⁹ We used frequency modulated recording of ST segments to determine the frequency of symptomatic and asymptomatic ischaemic episodes, and differences in time course, heart rates, and time of appearance of different types of ischaemic episode in patients with confirmed or suspected coronary heart disease.

Patients and methods

We studied 296 consecutive patients who underwent cardiac catheterisation and coronary angiography at this hospital between January and July 1982. Patients with atrial fibrillation, left or right bundle branch block (which interfere with Holter analysis of ST segments), valvar heart disease, and cardiomyopathy were excluded. There were 241 male patients (81%, mean age 52.9 years, range 21-73) and 55 female patients (19%, mean age 54.9 years, range 33-69).

Of the 296 patients, 67 (22.6%) had no major coronary artery stenosed by more than 50%, 55 (18.6%) had single vessel disease, 61 (20.6%) had double vessel disease, and 113 (38.2%) had triple vessel disease. Hypokinesia or akinesia was shown in the left ventriculogram in 132 patients (44.6%).

ST SEGMENT MONITORING

Electrocardiographic monitoring was carried out for 24 hours on the day before coronary angiography when patients were in hospital and walking about. Calcium channel blockers and long acting nitrate medications were stopped the day before the record-

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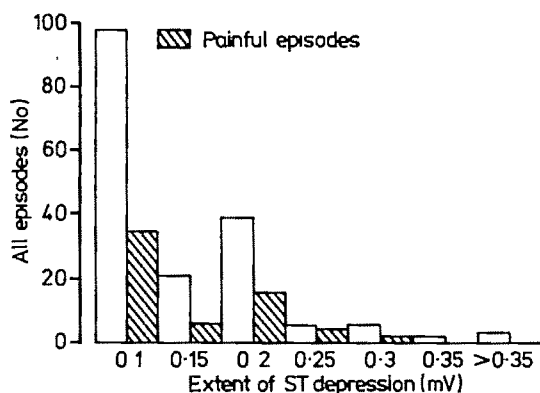


Fig. 1 Number of episodes of ST depression and extent of ST depression. The proportion of painful episodes is not significantly greater with deeper ST depression (≥ 0.2 mV).

ing. Short acting nitrates were used to alleviate angina, and beta blockers were continued at the patient's usual dose.

The frequency modulated, calibrated recording system Medilog II (Oxford Electronics) was used with CC5 and CM5 leads as described by Balasubramanian *et al.*⁸ With the Oxford Medilog analysis system in the Holter mode we identified episodes of ST segment deviation visually and obtained analogue recordings at 25 mm/s. Recordings were taken of the beginning of an episode, 1 minute before the episode, when ST segment deviation was at a maximum, and at the end of the episode. Episodes were counted if there was ST segment deviation of at least 1 mm (0.1 mV) for at least one minute. An increase in heart rate preceding the episode was defined as an increase of 10% or more from one minute before to the start of the episode. Patients were asked to register painful events either by pressing the event button of the electrocardiographic recorder or by writing a note in a purpose made diary. All data from the electrocardiographic analysis were collected on a special sheet for further evaluation by computer. We noted the time lost from a full 24 hour recording because of artefacts, loose electrodes, or early removal of electrodes. No time was lost in recordings from 49% of the patients, and in recordings from another 24% there were losses of less than two hours. Losses of more than six hours led to exclusion, and a repeat recording was made where possible. The mean recording period for all patients was 22.6 hours.

DATA AND STATISTICAL ANALYSIS

All results were analysed by computer, by means of a data bank system developed at the Institut für Informationsverarbeitung, Statistik und Biomathe-

matik in our institution.¹⁰ We used the χ^2 test to evaluate differences between groups.

Results

FREQUENCY OF DIFFERENT EPISODES AND PAIN AND DEGREE OF ST DEPRESSION

Seventy of the 296 patients studied had episodes of transient ST segment changes. We recorded 221 episodes in 50 (71.4%) male and 20 (28.6%) female patients. One hundred and sixty five (74.7%) episodes were ST depression and 56 (25.3%) were ST

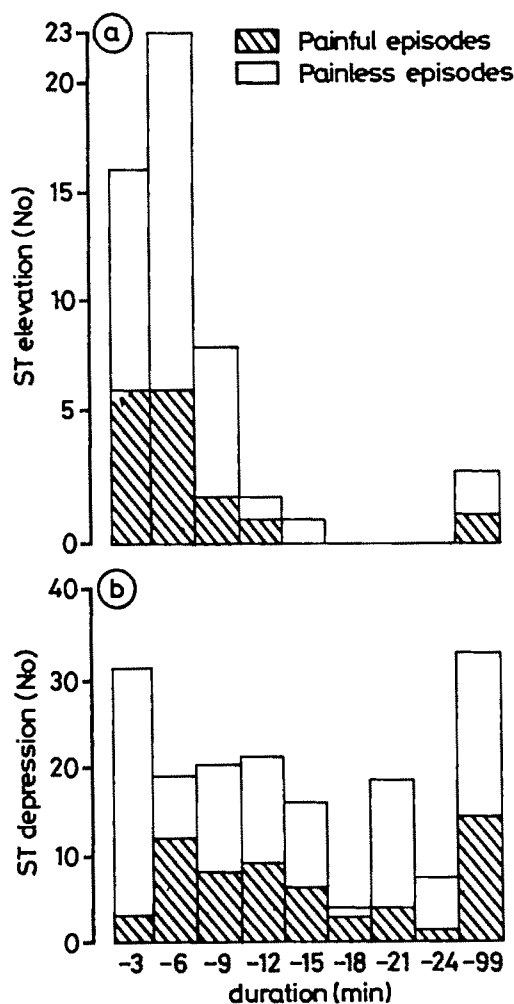


Fig. 2 Number of episodes of ST elevation (a) and ST depression (b) by duration of the episode (< 10 minutes or ≥ 10 minutes). There were more short episodes with ST elevation ($p < 0.001$). The proportion of painful episodes is not significantly greater with longer episodes (> 10 minutes).

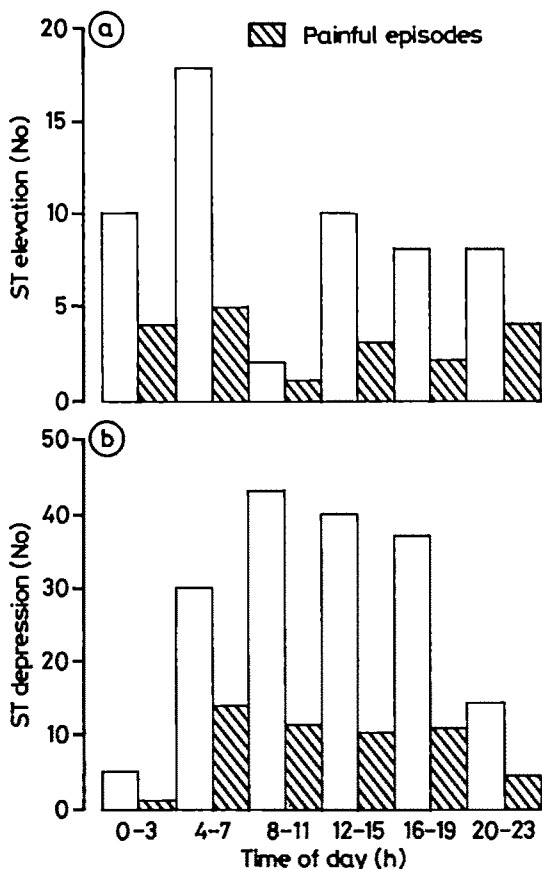


Fig. 3 The time of day at which episodes of ST elevation (a) and ST depression (b) occurred. ST elevation was most common during the early morning and there was a broad daytime peak for ST depression. The occurrence of pain was not related to the time of day.

elevation. Pain was reported during 77 (34.8%) episodes. Similar percentages of painful episodes occurred during ST elevation ($n=19$, 33.9%) and ST depression ($n=58$, 35.2%).

The degree of ST depression did not correlate with the occurrence of pain (Fig. 1). Of 118 episodes of 0.1 or 0.15 mV ST depression, 39 (33.1%) were painful and (19 (40.4%)) of 47 episodes with ST depression of ≥ 0.2 mV were painful (χ^2 , NS).

DURATION AND TIME OF APPEARANCE

There were significantly more episodes of ST elevation of short duration (<10 minutes) and significantly more episodes of ST depression of long duration (≥ 10 minutes) (χ^2 , $p < 0.001$). The occurrence of pain during an episode did not correlate

with the duration of the episode. Many short episodes were associated with pain and many long episodes were not associated with pain (χ^2 , NS). The depth of ST depression was not correlated to the duration of an episode. An increase in heart rate was significantly more common when episodes lasted more than 10 minutes ($p < 0.05$).

We also compared the duration of anginal attacks as perceived by the patients with the duration of their transient ischaemic episodes. Of the patients, 71.6% reported that angina lasted from one to five minutes, yet most ischaemic episodes lasted for seven minutes or longer (92 of 140 episodes, 65.7%). Thus not only do many transient ST changes pass unnoticed by the patient, but also the duration of the ischaemic episode is usually symptomatically underestimated.

ST elevation was most frequent late at night and early in the morning (Fig. 3). This diurnal difference was significant when frequencies from 8 am to 8 pm and from 8 pm to 8 am were compared ($p < 0.001$). Also there were significantly more short episodes

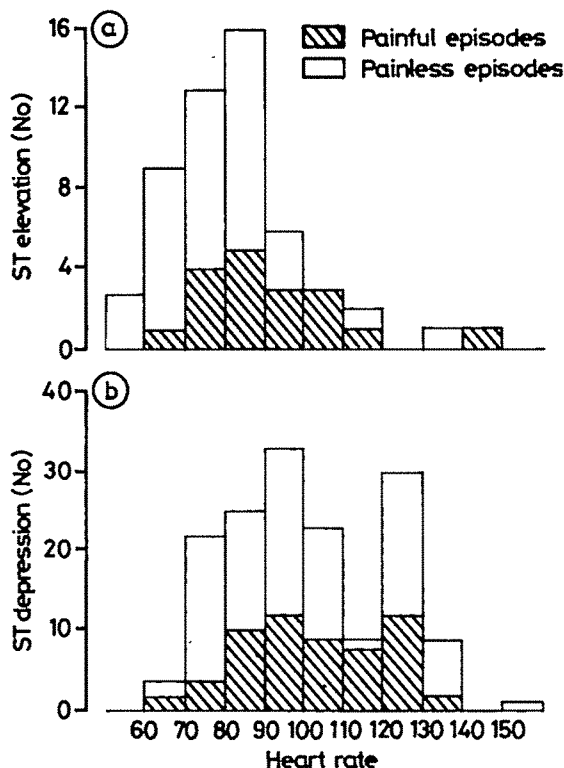


Fig. 4 Number of episodes of ST elevation (a) and ST depression (b) by heart rate at which ischaemia became apparent. Most episodes with ST elevation occurred at heart rates below 90 beats/min.

($p < 0.05$) and episodes without tachycardia ($p < 0.025$) during the night. The time of day did not correlate with the occurrence of pain. The diurnal distribution of ST depression without increased heart rate resembled the distribution of ST elevation.

ST ELEVATION OR ST DEPRESSION AND HEART RATE CHANGES

ST elevation started at significantly lower heart rates (90 beats/minute or less) than did ST depression ($p < 0.001$) (Fig. 4). Pain during episodes of ST elevation and ST depression did not correlate with heart rate. Heart rate increased by 10 beats or more one minute before the start of ST changes in 110 of 165 episodes with ST depression (66.7%) and in only six of 56 episodes with ST elevation (10.7%, $p < 0.001$).

Discussion

TRANSIENT ST CHANGES, ANGINAL PAIN, AND MYOCARDIAL ISCHAEMIA

We studied patients who are typical of those encountered in clinical practice. We consecutively investigated all patients undergoing coronary arteriography in our institution. This approach differs from the more selective procedures of other studies³⁻⁵ and provides information about the incidence of transient electrocardiographic changes in an "unselected" group of patients with confirmed or suspected coronary artery disease. Recordings were done while the patients were in hospital but able to walk about. The results may differ from those in patients at home or work. Just under a quarter of our patients showed transient ST segment changes during one day of ambulatory recording.

Anginal attacks accompanied by ST elevation are said to define Prinzmetal's variant angina.¹¹ Yet invasive studies showing impaired coronary flow and ventricular function together with electrocardiographic changes and pain have shown that pain is a late and sometimes insensitive indicator of ischaemia.¹² Nor is pain a consistent finding during episodes of ST depression caused by ischaemia.^{4,13,14} In patients with silent ischaemia there may be a disturbance of pain perception,^{15,16} and painless myocardial infarctions are common and have a poor prognosis.¹⁷ The clinical importance of painless ST changes is controversial because such changes can occur in normal healthy volunteers.¹⁸⁻²⁰ Until the cause of such ST changes in otherwise normal people is known, false positive results will be found when normal populations are screened. These changes are rare, however, in the age group in which most patients with coronary dis-

ease occur.²⁰ Painful and painless episodes associated with similar ST deviations occurred in the same individual. Thus the ST segment changes are unlikely to be artefacts or normal findings.

DIFFERENCES BETWEEN EPISODES OF ST ELEVATION AND ST DEPRESSION IN DURATION, DIURNAL DISTRIBUTION, AND HEART RATES

In our patients episodes of ST elevation were shorter than episodes of ST depression. This suggests that the pathophysiological mechanisms underlying ST elevation and ST depression follow different time courses. There were no differences in pain frequency with shorter or longer episodes and ST depression was not deeper with longer episodes. The duration of an episode does not therefore seem to reflect severity of ischaemic changes.

ST elevations were most frequent in the early morning. This finding has also been described by others^{21,22} and may relate to the circadian variation of disease activity in variant angina.²³ Parallels have been drawn with phases of rapid eye movement sleep in patients with variant angina²⁴ but the interrelations of disease activity and circadian rhythm are still speculative and need further study. In patients with very severe fixed coronary disease, nocturnal ST depression may still be brought about by increased oxygen demand.²⁵ The typical diurnal distribution of episodes of ST elevation was found in our patients, although they had not given a clear cut history of such a pattern for their angina.

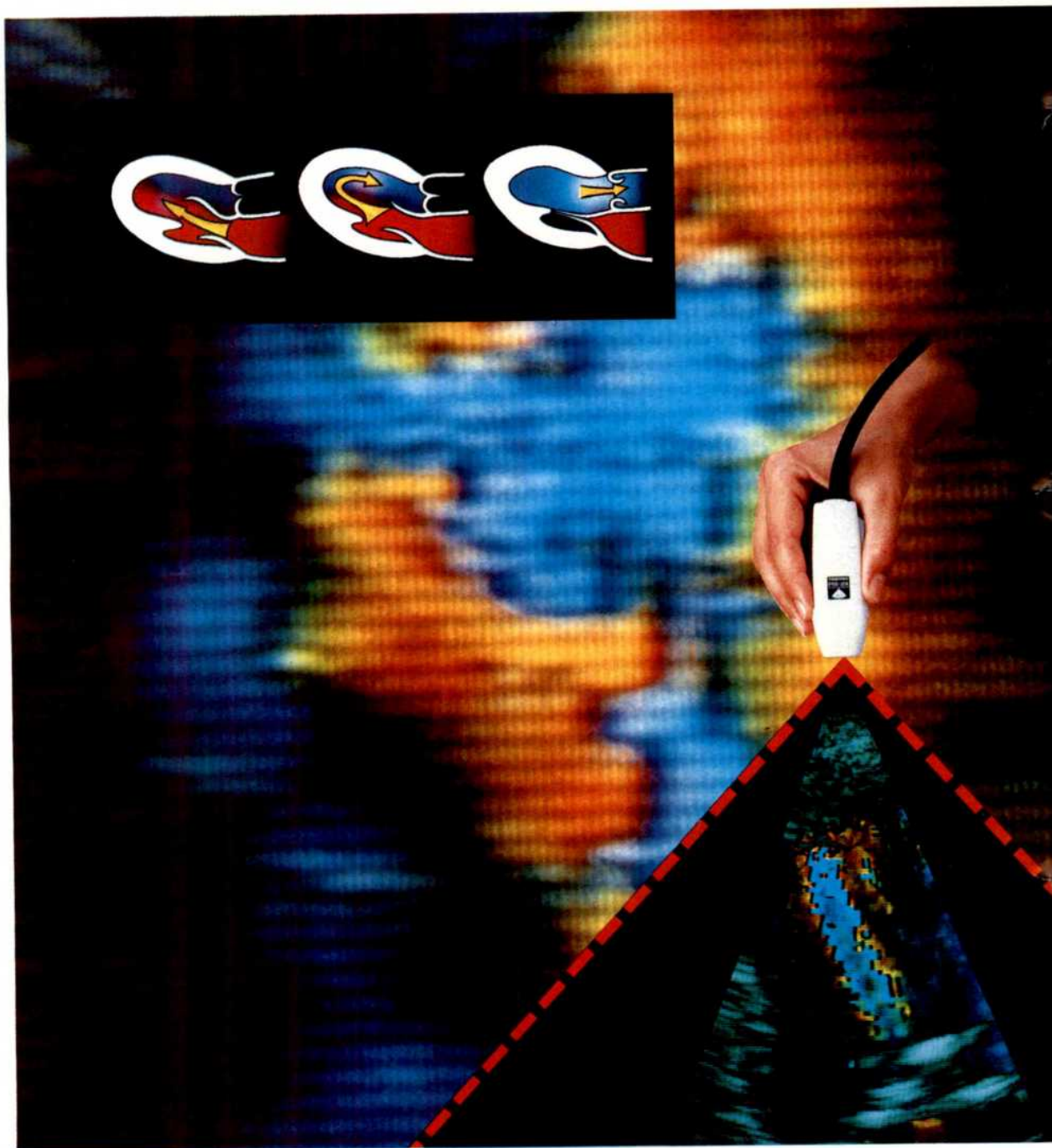
ST elevation occurred at lower heart rates than ST depression. This accords with the suggested explanation of a reduction in myocardial blood supply for episodes of ST elevation, while in ST depression with tachycardia increased oxygen demand is a more likely trigger. Continuous intra-arterial pressure monitoring in ambulatory patients^{26,27} showed that in spontaneous ischaemic episodes the rate-pressure product was consistently lower than in exercise induced ischaemia in the same patients. Therefore factors other than increased oxygen demand must be instrumental in precipitating ischaemic episodes.

In our study we found considerable overlap of duration, diurnal distribution, and heart rates in episodes of ST elevation and ST depression. This makes a combination of factors the most likely explanation for the induction of transient ischaemic ST segment changes in many instances.

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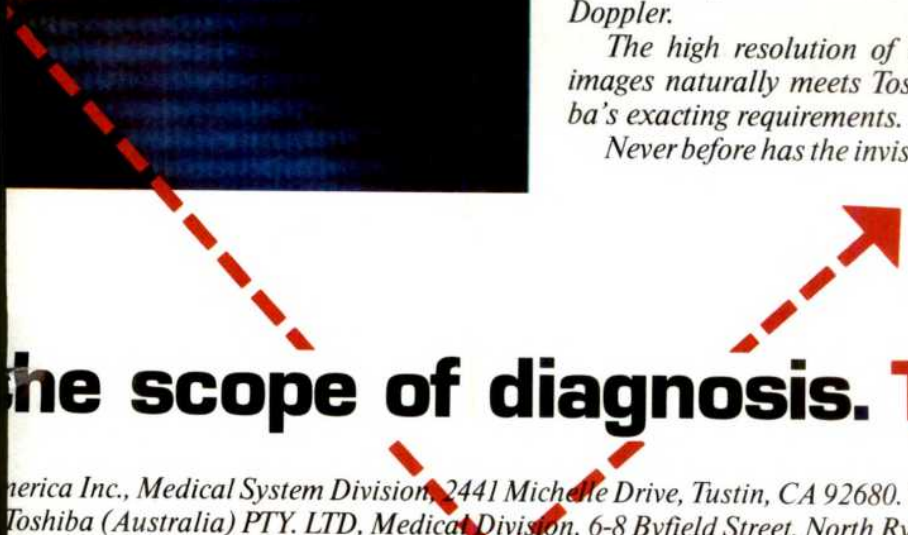
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Bypass grafting to the right coronary artery with and without endarterectomy: patency at one year

P H KAY, N BROOKS, P MAGEE, M F STURRIDGE, R K WALESBY,
J E C WRIGHT

From the London Chest Hospital, London

SUMMARY Between January 1979 and December 1981, 142 patients undergoing surgery to the right coronary artery agreed to have repeat coronary arteriography one year later. Thirty patients underwent combined endarterectomy and bypass grafting to the right coronary artery. The patency of these grafts was compared with that of grafts in 69 patients undergoing direct grafting to the right coronary artery and in 43 with grafting to the posterior descending coronary artery. There were two hospital deaths and one late death. No patients developed new inferior Q waves on the electrocardiogram. Repeat coronary arteriography at one year showed that 21 (72%) of the 29 grafts were patent after combined endarterectomy and bypass grafting to the right coronary artery. Sixty three (94%) grafts to the right coronary artery and 40 (93%) grafts to the posterior descending coronary artery were patent at one year. Direct grafts to the right coronary artery or its posterior descending branch had a significantly higher patency rate at one year than grafts to the endarterectomised right coronary artery.

Graft patency after the combined procedure correlated with the extent of atherosclerosis in the posterior descending coronary artery. It was not influenced by treatment with platelet antagonists. Endarterectomy of the right coronary artery was most successful when it allowed a single graft to perfuse both the large posterior descending and left ventricular branches.

Coronary artery bypass grafting is now the treatment of choice for symptomatic patients with severe left main stem disease.^{1,2} Patients with chronic stable angina and minimal impairment of left ventricular function with either triple vessel disease^{3,4} or double vessel disease involving the proximal third of the left anterior descending coronary artery⁴ may also have an improved survival after coronary artery surgery. Moreover, coronary artery bypass grafting provides excellent pain relief for those patients with less widespread atheroma whose angina proves refractory to medical treatment.⁵

Isolated coronary endarterectomy was first described in 1957.⁶ The later combination of endarterectomy and coronary artery bypass grafting has widened the scope of myocardial revascularisation in patients with diffuse coronary disease.⁷⁻¹⁴ This technique is suitable particularly for the right

coronary artery which is straighter than the left and surgically accessible to the level of its posterior descending branch.

There have been several retrospective reports of graft patency after combined endarterectomy and coronary artery bypass grafting to the right coronary artery.^{7-11,13,14} We present a prospective study of 30 patients undergoing combined endarterectomy and bypass grafting to the right coronary artery. The results are compared with those of similar groups of patients undergoing grafts to the right coronary artery or its posterior descending branch.

Patients and methods

From January 1979 to December 1981 approximately 750 patients underwent isolated coronary artery surgery at the London Chest Hospital. All patients aged less than 70 years and who were able to tolerate aspirin were approached and asked to take part in a prospective trial entailing elective repeat coronary arteriography at one year. We report the results in the 142 patients undergoing surgery to the

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Accepted for publication 9 July 1985

Table 1 Preoperative clinical characteristics

	RCA-VG (n=69)	PDA-VG (n=43)	E-RCA-VG (n=30)
Mean age	55	52	55
Angina grade (mode)	3	3	3
Smoker	38 (55%)	25 (58%)	14 (47%)
Diabetes	4 (6%)	5 (12%)	4 (13%)
Hypertension	10 (15%)	6 (14%)	8 (27%)
Hyperlipidaemia*	2 (3%)	7 (16%)	12 (40%)
Myocardial infarction	43 (62%)	27 (63%)	20 (67%)
LV asynergy (angiography)	53 (77%)	31 (72%)	22 (73%)

LV, left ventricular; RCA-VG, right coronary artery vein graft; PDA-VG, posterior descending coronary artery vein graft; E-RCA-VG, endarterectomy and RCA-VG

*E-RCA-VG vs RCA-VG, $p < 0.05$; E-RCA-VG vs PDA-VG, $p < 0.05$

right coronary artery who fulfilled these criteria. In all cases the right coronary artery was angiographically dominant and gave rise to the posterior descending artery.

The mean age of the patients was 54 years (range 28–68) and the male to female ratio was 8:1. All patients presented with angina (mode of grade III on the New York Heart Association Classification). Their preoperative clinical characteristics are shown in Table 1. Only one clinical variable, the incidence of hyperlipidaemia, was significantly more common in the group of patients undergoing combined endarterectomy and bypass grafting to the right coronary artery ($p < 0.05$).

OPERATIVE DETAILS

The operative technique was left to the discretion of the individual surgeon. Cardiopulmonary bypass was established between the right atrium and the ascending aorta. In 124 patients the distal anastomoses were constructed during short periods of elective ventricular fibrillation with the aorta cross clamped, the nasopharyngeal temperature having drifted to 32°C. In 18 patients the distal anastomoses were constructed during a single period of cold cardioplegic arrest with the oesophageal temperature at 28°C. The number of grafts of greatest frequency was three per patient (range 2–5). The choice of surgical procedure for grafting the right coronary artery was determined by its angiographic appearance. In all cases the anastomosis was constructed using a continuous suture of 6/0 Prolene.

Coronary artery bypass graft to the right coronary artery (RCA-VG)—Sixty nine patients with proximal disease in the right coronary artery and a distal vessel of good angiographic appearance underwent direct saphenous vein grafting to the right coronary artery.

Coronary artery bypass graft to the posterior descending coronary artery (PDA-VG)—Forty three patients with widespread atheroma of the main right coronary artery but a disease free posterior

descending branch greater than 1 mm in diameter underwent direct grafting into the posterior descending artery.

Combined endarterectomy and bypass graft to the right coronary artery (E-RCA-VG)—Thirty patients underwent combined endarterectomy and bypass grafting to the right coronary artery. This included nine patients with occlusive disease at the crux in whom a successful endarterectomy allowed a single graft to perfuse both posterior descending and left ventricular branches. In a further nine patients the decision to perform an endarterectomy was made after the right coronary artery had been opened. In twelve patients the posterior descending artery was too diffusely diseased to be grafted.

TECHNIQUE OF ENDARTERECTOMY

In every instance a mechanical endarterectomy was performed, though the technique varied with the individual operator. The acute margin of the heart was retracted to expose the distal right coronary artery. A 1 cm incision was made 1 cm proximal to the origin of the posterior descending branch and the correct endarterectomy plane in the media was established. The atheromatous core was first mobilised proximally by means of a combination of mechanical traction with De Bakey forceps and blunt dissection with a Watson-Cheyne dissector. Usually when 2 cm of the core had been mobilised proximally it was divided cleanly with scissors. A similar technique of traction with the forceps and dissection with the dissector was used to mobilise the core distally and free the posterior descending and left ventricular branches. The core was then withdrawn by exerting traction on it with forceps and counter traction on the epicardium with a second pair of forceps. The patency of the distal vessels was confirmed by the passage of a 1 mm probe. In one case the core broke and was retrieved by a second arteriotomy in the posterior descending artery. In this case the graft was anastomosed to the posterior descending artery and the right coronary artery was closed with a vein

Table 2 Hospital mortality and morbidity

	RCA-VG (n=69)	PDA-VG (n=43)	E-RCA-VG (n=30)	Total (n=142)
No of grafts per patient (mode and range)	3 (2-5)	3 (2-5)	3 (2-4)	3 (2-5)
Mortality	1 (1.4%)	0	1 (3.3%)	2 (1.4%)
New inferior Q waves	0	0	0	0

RCA-VG, right coronary artery vein graft; PDA-VG, posterior descending artery vein graft; E-RCA-VG, endarterectomy and RCA-VG.

patch.

In addition the 142 patients received a total of 306 grafts to the left coronary system. Endarterectomy was not performed on any branches of the left coronary artery.

All patients were given warfarin anticoagulation for three months from the second postoperative day to maintain a prothrombin time of between 24 and 30 seconds. In addition, the patients were randomised according to the double blind protocol of one of the authors (NB) to receive either aspirin 990 mg and dipyridamole 225 mg daily or placebo for twelve months from the first postoperative day. Thirty two (48%) patients received platelet antagonists after right coronary artery grafting, 23 (53%) after grafts to the posterior descending artery, and 16 (53%) after combined endarterectomy and bypass grafting to the right coronary artery.

FOLLOW UP

All surviving patients were admitted to the London Chest Hospital for elective recatheterisation a mean of 12 months (range 11-14) after the operation.

STATISTICAL ANALYSIS

Fisher's exact test was used for statistical analysis, the level of significance being set at $p < 0.05$.

Results

HOSPITAL MORTALITY AND MORBIDITY

Two patients died within 30 days of operation, one after a graft to the right coronary artery (mortality after RCA-VG 1.4%) and the second after a combined endarterectomy and bypass grafting to the right coronary artery (mortality after E-RCA-VG

3.3%). Although seven (5%) of the 140 operative survivors developed new Q waves on the electrocardiogram indicating perioperative myocardial infarction, none of these was in the inferior position. The distribution of these events is summarised in Table 2.

LATE RESULTS

There was one late death from a myocardial infarction six months after triple coronary artery bypass grafting which included the right coronary artery. Thus, the one year survival of the total group of 142 patients was 98%.

A second patient who had undergone right coronary artery grafting had a late anterior myocardial infarction associated with occlusion of the anterior descending graft.

Fifteen (11%) patients complained of residual angina (nine grade I, four grade II, and two grade III, New York Heart Association classification). The two patients with more severe angina have undergone repeat myocardial revascularisation. These late results are summarised in Table 3.

GRAFT PATENCY

Elective coronary arteriography was performed in the 139 surviving patients a mean of 12 months after operation. Sixty three (94%) of the 67 grafts to the right coronary artery and 40 (93%) of the 43 grafts to the posterior descending artery were patent, as were twenty one (72%) of the 29 grafts in patients who had undergone combined endarterectomy and bypass grafting to the right coronary artery (patency RCA-VG *vs* E-RCA-VG, $p < 0.01$; patency PDA-VG *vs* E-RCA-VG, $p < 0.01$).

Table 3 Results at one year

	RCA-VG (n=68)	PDA-VG (n=43)	E-RCA-VG (n=29)	Total (n=140)
Late mortality	1 (1.5%)	Nil	Nil	1 (0.7%)
Late myocardial infarction	2 (2.9%)	Nil	Nil	2 (1.4%)
Recurrent angina	5 (7%)	3 (7%)	7 (24%)	15 (11%)

RCA-VG, right coronary artery vein graft; PDA-VG, posterior descending artery vein graft; E-RCA-VG, endarterectomy and RCA-VG.

Table 4 Relation between graft occlusion and infarction or recurrent angina

Graft	Myocardial infarction			Recurrent angina		
	Graft occlusion			Graft occlusion/stenosis		
	Right	Left	Right + left	Right	Left	Right + left
RCA-VG*	0	4	0	1	3	1
PDA-VG	0	2	0	0	2	1
E-RCA-VG	0	2	0	5	1	1

*Excludes one patient who died after a late myocardial infarction.

RCA-VG, right coronary artery vein graft; PDA-VG, posterior descending artery vein graft; E-RCA-VG, endarterectomy and RCA-VG

Thirty (94%) of grafts to the right coronary artery in the thirty two patients taking aspirin and dipyridamole were patent at one year, compared with 33 (94%) in the 35 control patients. Grafts to the posterior descending artery were patent in 21 (91%) of the 23 patients on antiplatelet treatment and in 19 (95%) of the 20 patients who were not on platelet antagonists. Twelve (75%) of the grafts to the endarterectomised right coronary artery were patent in the 16 patients taking aspirin and dipyridamole, compared with nine (69%) in the 13 control patients.

Two hundred and sixty four (88%) of the 301 grafts anastomosed to the left coronary circulation were patent at one year in surviving patients. The results were similar in each of the three groups. There was no correlation between occlusion of grafts to the right coronary artery and those to the left coronary system.

Forty one (29%) of the 139 surviving patients had one or more occluded grafts. They included the eight surviving patients who had perioperative or late myocardial infarctions and 13 of the 15 patients continuing to experience angina. The other two cases of late angina had evidence of graft stenosis at the coronary anastomosis. There were no other cases of graft stenosis at the coronary anastomosis.

Fifteen patients had occluded grafts to the right coronary artery. In no case did this lead to the development of new inferior Q waves. All perioperative or late myocardial infarctions were associated with occlusion of a graft to the left coronary system. Nine (60%) of the 15 patients with occluded right coro-

nary artery grafts continued to experience angina; these were predominantly in the group who had undergone endarterectomy. The relation between graft occlusion/stenosis and myocardial infarction and recurrent angina is shown in Table 4.

ANALYSIS OF ENDARTERECTOMY RESULTS

Patients undergoing combined endarterectomy and bypass grafting to the right coronary artery were divided into two subgroups according to suitability of the posterior descending branch for grafting. The results for these two subgroups are outlined in Table 5. Sixteen (89%) of the 18 patients with a large posterior descending artery had patent right coronary artery grafts after combined endarterectomy and bypass grafting. This figure is not significantly different from the 93% patency rate in patients who had undergone direct grafting to the posterior descending artery. Conversely, in the subgroup of patients in whom the posterior descending artery was unsuitable for grafting five (45%) grafts were patent and five (45%) of the 11 surviving patients continued to experience low grade (New York Heart Association grade I or II) angina.

Discussion

In this prospective study we attempted to define the best surgical approach to the diseased right coronary artery as assessed by graft patency at one year. Though we studied a selected group of patients, selection was purely in terms of patient compliance rather than clinical variables. Indeed, the pre-operative clinical characteristics of our patients were similar to those in another series.¹²

The overall early results, with a 1.4% hospital mortality and a 5% incidence of perioperative myocardial infarction, are similar to those reported by other centres.¹⁵⁻¹⁷ Three hundred and sixty seven (89%) of the 411 grafts performed without endarterectomy were patent at a mean of 12 months after the operation. This level of graft patency is higher than that reported by other centres.¹⁸⁻²¹

Two patients had late myocardial infarctions, one of which was fatal, while 15 other patients experi-

Table 5 Results of endarterectomy and right coronary artery vein grafting

	Large (>1 mm) PDA (n=18)	PDA ungraftable (n=12)
Hospital mortality	0	1 (8%)
Late mortality	0	0
Late infarction	0	0
Recurrent angina	2 (11%)	5 (45%)
Graft patency	16 (89%)	5 (45%)

PDA, posterior descending artery.

enced residual angina. In each instance there was graft failure (occlusion in 14 cases and stenosis at the coronary anastomosis in two cases) rather than progression of distal disease in the native vessels. Thus, in the presence of complete myocardial revascularisation, recurrence of symptoms in the first year signified graft failure. The converse, however, did not necessarily apply since 20 (49%) patients with graft occlusion were symptom free and had no new ischaemic changes on the electrocardiogram.

This paper confirms that endarterectomy of the right coronary artery can be performed safely with no significant increase in hospital mortality,^{7,10,12,13} and in this series there was no associated inferior myocardial infarction. The 6.7% incidence of peri-operative infarction was associated only with occlusions of left sided grafts. Thus, unlike Miller *et al*¹² we did not demonstrate an increased incidence of myocardial damage after endarterectomy. The long term results, however, with seven (24%) of the 29 surviving patients continuing to experience angina compared with five (7%) of the 68 patients who had undergone direct grafting to the right coronary artery ($p < 0.05$) indicate that this technique may be less beneficial. This result accorded with a significant difference in the patency rate of the right coronary grafts in the group without endarterectomy (94%) and the group with endarterectomy (72%) ($p < 0.01$). Thus, the overall results of combined endarterectomy and bypass grafting to the right coronary artery appear at first sight to be inferior to those of direct grafting on to the right coronary artery itself.

Patients undergoing combined endarterectomy and bypass grafting to the right coronary artery were composed of two subgroups; those with a large (> 1 mm) disease free posterior descending artery which was suitable for grafting and those in whom the posterior descending artery was unsuitable for grafting either because of its small size or because extensive disease was present. The results of combined endarterectomy and bypass grafting in patients with a graftable posterior descending artery and direct grafting of the posterior descending artery were not significantly different. The 89% patency rate for the combined procedure in this subgroup compares favourably with that reported in other series.^{7,9-11,13,14} These good results are balanced by the poor results of endarterectomy in patients with small (< 1 mm) or heavily diseased posterior descending arteries in whom only 45% grafts were patent at one year (Table 5). Clearly, these subgroups represent extreme ends of a spectrum of disease. Comparison of results from different centres will be greatly influenced by the distribution of these subgroups within a given

series.

Information in previous reports of combined endarterectomy and bypass grafting has always been gathered retrospectively.^{7,9-14} The aim of endarterectomy has been loosely stated as being to increase the scope of myocardial revascularisation, though the size of the distal vessels has not been given. Both Miller *et al*¹² and Keon²² suggest that a direct graft to the distal vessel is preferable to endarterectomy, though neither supports this with data on graft patency. Keon sets a lower limit of 1.5 mm on the size of the posterior descending artery which is suitable for grafting.²² We believe that our data suggest that this figure can now be reduced to 1.0 mm.

Our results did not show a beneficial effect of platelet inhibiting drugs on graft patency in any of the three operative groups. This was particularly surprising in the endarterectomy group and was in direct contrast to Chesebro *et al*'s conclusions.¹⁹ There are several differences, however, between the two trials. In the American series dipyridamole therapy was started before operation and aspirin was added on the day of operation. In our series platelet inhibiting drugs were started after removal of the chest drains on the first postoperative day. This treatment was supplemented with warfarin anticoagulation for three months. The patency of grafts to the non-endarterectomised right coronary artery or its posterior descending branch was 95% in our placebo group. This was similar to the 97% patency in Chesebro's treated group and significantly higher than the 80% patency of his control group. Thus, it is probable that the beneficial effects of aspirin and dipyridamole were masked by the three month period of anticoagulation.

The dilemma of whether it is better to perform an endarterectomy on a large (3-4 mm) right coronary artery before saphenous vein grafting or to anastomose the graft directly to a posterior descending artery 1.0-1.5 mm in diameter remains unresolved. The position is further complicated when there are two large disconnected distal branches of the right coronary artery, as there were in eleven patients in the series. Nine patients were treated by combined endarterectomy and bypass grafting which allowed both branches to be perfused by a single graft. The other two patients were treated by individual grafts to the posterior descending artery and distal left ventricular branch. All these grafts were patent at re-examination. Thus, the tendency to perform combined endarterectomy and bypass grafting will remain idiosyncratic.

Conclusions

We have now adopted the following surgical ap-

proach on the basis of both preoperative assessment and direct inspection of the right coronary artery at operation: (a) Our first choice of procedure is a direct graft to the main coronary artery. (b) If the right coronary artery is unsuitable for grafting attention is turned to its posterior descending branch. A graft to this artery gives equally good results at one year. (c) Occlusive disease of the crux of the right coronary artery with a large posterior descending branch may be satisfactorily treated by combined endarterectomy and bypass grafting. This approach results in a similar patency rate to that of direct grafts to the posterior descending artery and has the advantage that a single graft perfuses both posterior descending and left ventricular branches. If the posterior descending artery is unsuitable for grafting the results of combined endarterectomy and bypass grafting to the right coronary artery are poor with a low graft patency and a high frequency of recurrent angina.

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Quantification of intracardiac shunts by gold-195m, a new radionuclide with a short half life

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SUMMARY Gold-195m, a radionuclide with a short half life (30.5 s) was used to quantify left to right intracardiac shunts. The results of this method were compared with those obtained with technetium-99m, a method that was validated against oximetry. In five patients the pulmonary to systemic flow ratio ($> 3:1$) obtained by both radionuclides indicated that the level of shunting was too high to be measured accurately. In one patient fragmentation of the bolus meant that no satisfactory gamma fit could be obtained. In the remaining 16 patients there was no significant difference between two successive ^{195m}Au studies. The agreement between ^{99m}Tc results and ^{195m}Au results was excellent. Oxygen administration, straight leg raising exercise, and the use of oblique projections did not affect the values of the pulmonary to systemic flow ratio. The technique of quantification of intracardiac shunts by ^{195m}Au gives reproducible and accurate results and the low radiation dose means that it is suitable for use in children with suspected left to right shunts.

In recent years the quantification of intracardiac left to right shunts by radionuclide techniques has been successfully applied to children and adults.¹⁻⁶ In this paper we compare the results obtained with gold-195m, a new radionuclide with a short half life (30.5 s) generated from mercury-195m,⁷ with those obtained with a technetium-99m sodium pertechnetate technique which we have validated against oximetry.

The low radiation dose of ^{195m}Au means that several studies may be performed in the same patient. We have determined the feasibility of using ^{195m}Au with a standard single crystal gamma camera and have assessed the effects of interventions on the results obtained.

Patients and methods

PATIENTS

We studied 22 patients aged 6-63 years (mean 22.5) (Table 1). In all left to right intracardiac shunts were suspected. Informed consent was obtained from every patient or their parents.

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Accepted for publication 22 July 1985

METHODS

The patients were studied by means of a Technicare ON100 gamma camera. An intravenous cannula was inserted into the antecubital vein, preferably of the right arm. The detector head of the camera was positioned over the lung field. A bolus of radionuclide, volume < 1 ml, was injected, followed by a 10-20 ml saline flush. Immediately after injection we started data acquisition with a Nodectest V77 computer. Seventy frames of 0.5 s duration were collected for subsequent processing. The mercury-195m/gold-195m generator was positioned in a shielded corner of the gamma camera room and injection therefore occurred almost immediately after elution of ^{195m}Au . Breakthrough of ^{195m}Hg was minimised by eluting the generator several times and discarding the eluates which contained higher quantities of ^{195m}Hg . This manoeuvre was also carried out if there was an interval of ≥ 2 minutes between consecutive elutions. At the time of injection the activity of ^{195m}Au was approximately 550 MBq. ^{99m}Tc was given on the basis of 5 MBq/kg body weight activity.

The data collected were recalled from disc and played back in cine film form. The frames of the pulmonary phase were then identified as was the frame in which the superior vena cava and right ventricle were well delineated. Two regions of inter-

Table 1 Pulmonary to systemic flow ratios in 22 patients with suspected left to right intracardiac shunts

Patient	Age	Au1	Au2	LAO	Oxygen	Exercise	^{99m} Tc	Diagnosis
1	11	>3	>3	>3	—	—	>3	ASD
2	20	>3	>3	>3	—	—	>3	ASD
3	8	2.1	2.2	3.0	3.2	—	2.2	ASD
4	7	1.6	1.6	1.6	—	—	1.5	VSD
5	7	1.1	1.1	1.1	—	—	1.0	ASD?
6	15	1.2	1.2	1.2	1.1	1.2	1.2	VSD
7	22	>3	>3	>3	—	—	>3	ASD
8	11	1.6	1.6	1.3	1.7	—	2.0	VSD
9	63	>3	>3	>3	—	—	>3	VSD and ASD
10	21	1.1	1.1	1.1	1.1	1.1	1.1	PS? ASD
11	26	Fragmented bolus		—	—	—	—	PDA?
12	35	1.1	1.1	1.1	1.1	1.1	1.1	VSD?
13	45	1.2	1.2	1.3	1.2	1.1	1.2	AV coronary fistula
14	7	1.8	1.8	1.7	1.9	1.8	1.7	ASD
15	35	1.2	1.2	1.2	1.1	1.1	1.4	VSD?
16	6	1.1	1.2	1.3	—	—	1.3	VSD
17	7	>3	>3	>3	—	—	>3	VSD
18	45	2.5	2.1	1.8	1.9	1.9	2.0	ASD
19	11	1.4	1.3	1.5	—	—	1.4	VSD
20	13	1.3	1.3	1.3	1.3	1.3	1.3	VSD
21	30	1.2	1.1	1.1	1.2	1.2	1.2	VSD
22	50	1.1	1.0	—	1.1	1.2	1.1	VSD?
Mean (SD)		1.4 (0.4)	1.38 (0.36)	1.44 (0.4)	1.44 (0.62)	1.3 (0.3)	1.42 (0.36)	

Au1, first gold-195m study; Au2, second gold-195m study; LAO, left anterior oblique; ASD, atrial septal defect; VSD, ventricular septal defect; AV arteriovenous, PS, pulmonary stenosis.

est were drawn: one over the superior vena cava avoiding the lung, and a second over the right lung avoiding the heart and superior vena cava. Activity-time curves were generated and the curve for the superior vena cava was examined to check the quality of the bolus. The lung curve was used to determine the pulmonary to systemic blood flow ratio ($Q_p:Q_s$) by means of a modification of the Maltz and Treves gamma variate fitting technique.⁵ If the bolus was fragmented or if its administration was unduly prolonged, and it was impossible to perform a satisfactory analysis, the study was rejected.

The method is designed to define a primary peak,

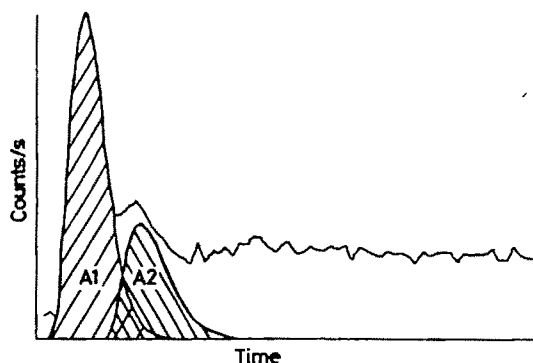


Fig. 1 Area under primary peak (A1) represents initial passage of radionuclide activity through lungs and area under secondary peak (A2) is attributable to premature recirculation caused by intracardiac shunting.

area A1, arising from the initial passage of activity through the lungs (Fig. 1) and a secondary peak, area A2, attributable to premature recirculation caused by shunting, which is superimposed on the descending slope of the primary peak. Activity arising from systemic recirculation appears towards the end of the curve.

The fitted primary peak is subtracted from the total curve and the operator may also fit the systemic recirculation curve which can also be subtracted. In our studies we only applied the recirculation correction if there was a clear recirculation peak. Finally A2 is obtained by fitting a curve to the shunt peak which has now been isolated. The ratio of pulmonary flow to systemic flow ($Q_p:Q_s$) is given by the formula:

$$A_2 \div (A_1 - A_2).$$

Statistics

All the results are expressed as mean (SD). Significant differences were assessed by the paired Student's *t* test and the Wilcoxon signed rank matched pairs test.

Validation

To validate our technique 20 patients who had previously undergone cardiac catheterisation were investigated by the ^{99m}Tc technique. The interval between the catheter and radionuclide studies ranged from two weeks to four months (mean 6.1 weeks). Ratio of pulmonary flow to systemic flow was calculated by oximetry (American Optical oximeter)

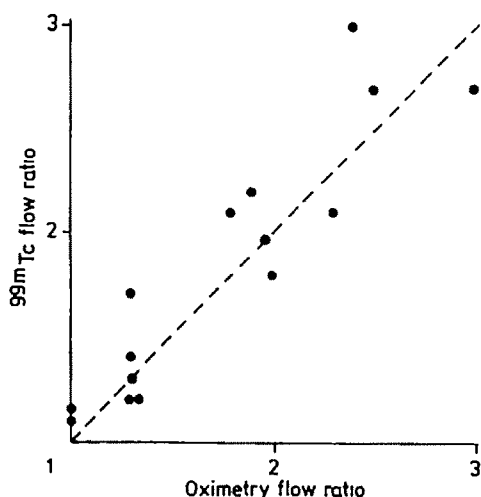


Fig. 2 Validation of flow ratios determined by ^{99m}Tc and oximetry in 15 patients with ratios of pulmonary flow to systemic flow of $< 3:1$.

during the catheter study. The saturation run in each case took less than 10 minutes. Mixed venous oxygen content in patients with atrial septal defects was derived from the superior (SVC) and inferior vena caval (IVC) oxygen contents by the formula⁸:

$$(3 \times \text{SVC content} + \text{IVC content}) \div 4$$

The agreement between ^{99m}Tc values and oximetry values was excellent (Fig. 2). In five patients the ratio of pulmonary flow to systemic flow was $> 3:1$ by both the ^{99m}Tc technique and oximetry. These results are not included in any of the graphical comparisons since quantification is inaccurate at this level of shunting. The mean deviation from the line of identity for the remaining 15 patients was $-0.13 (0.22)$.

In addition, ^{99m}Tc studies were performed on a further 17 patients with clinically normal hearts who were receiving ^{99m}Tc for bone scans. All ratios of pulmonary to systemic flow were in the range of $1.0\text{--}1.2:1$ (mean (SD) $1.09 (0.06)$).

Results

In one patient a satisfactory gamma fit could not be obtained because of fragmentation of the bolus. In five of the patients the ratio of pulmonary flow to systemic flow was $> 3:1$ in both anterior and left anterior oblique ^{99m}Tc studies. In the 16 remaining patients the results of two successive anterior view ^{195m}Au studies were compared (Fig. 3). Mean (SD) deviation from the line of identity was $0.03 (0.12)$. Fig. 4 compares the mean of results obtained from

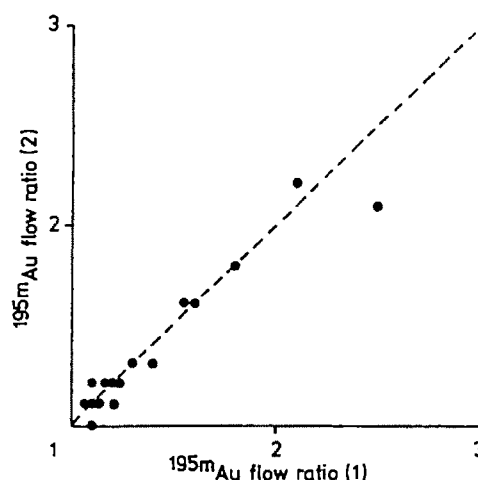


Fig. 3 Agreement between two sequential ^{195m}Au studies without intervention. Au1, first ^{195m}Au study; Au2, second ^{195m}Au study. Results from 16 patients with ratios of pulmonary flow to systemic flow of $< 3:1$ are shown.

the two ^{195m}Au studies with the ^{99m}Tc result. Mean deviation from the line of identity was $-0.02 (0.15)$. The mean ratio of pulmonary flow to systemic flow derived from the two ^{195m}Au studies was $1.40 (0.19):1$.

The mean ratio of pulmonary flow to systemic flow was $1.44 (0.49)$ in the 15 patients in whom the ratio was $< 3:1$ from the left anterior oblique projection.

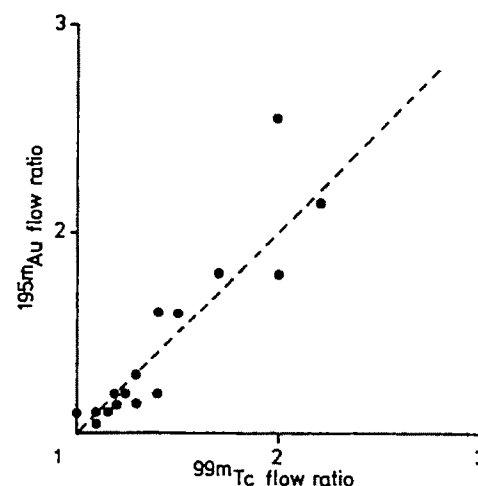


Fig. 4 A comparison between ratios of pulmonary flow to systemic flow measured by ^{195m}Au technique (mean of two studies) and ^{99m}Tc technique. Results from 16 patients with ratios of pulmonary flow to systemic flow of $< 3:1$ are shown.

Table 2 Dosimetry of typical injection of radionuclide derived from data given in MIRD^{8,12} and Ackers and de Jong¹¹

	^{195m} Au (550 MBq)		^{195m} Hg (120 kBq)		^{99m} Tc (370 MBq)	
	μSv	mrem	μSv	mrem	μSv	mrem
Heart wall	117	11.7	—	—	—	—
Kidneys	24	2.4	402	40.2	—	—
Lungs	84	8.4	26	2.6	—	—
Liver	18	1.8	36	3.6	—	—
Spleen	5	0.5	45	4.5	—	—
Gonads	8	0.8	26	2.6	900	90
Bladder wall	—	—	—	—	8500	850
Stomach	—	—	—	—	5100	510
ULI	—	—	—	—	12000	1200
LLI	—	—	—	—	11000	1100
Red marrow	—	—	—	—	1700	170
Thyroid	—	—	—	—	13000	1300
Total body	6	0.6	19	1.9	1100	110
Effective whole body	27	2.7	58	5.8	4120	412

ULI, upper large intestine; LLI, lower large intestine.

This was not significantly different from the value found in the anterior projection. It was impossible to identify the site of shunting from the cine display.

Twelve patients were studied after oxygen administration and ten after exercise. The mean ratio of pulmonary flow to systemic flow was 1.49 (0.62) after oxygen and 1.3 (0.3) after exercise. These were not significantly different from the resting values.

DOSIMETRY

To assess the radiation risk arising from the use of ^{195m}Au the effective whole body dose equivalent (the dose to the uniformly irradiated whole body that carries the same risk as the observed non-uniform dose) was calculated using the weighting factors recommended by the International Commission on Radiological Protection.⁹ In our generator system, which resembles that described by Elliott *et al.*,⁷ we measured a mean (SD) ^{195m}Hg breakthrough of 96 (24) kBq ^{195m}Hg per injection (n = 6), with a maximum of 120 kBq. Data for the dosimetry of ^{195m}Au and ^{195m}Hg in animals have been published.^{10,11} The data we used were taken from Ackers and de Jong.¹¹ Table 2 compares the dose from a

single injection of ^{195m}Au with that from a typical injection of ^{99m}Tc labelled sodium pertechnetate.¹² Table 3 compares the effective whole body dose equivalent from five injections of ^{195m}Au with that from a single injection of 370 MBq ^{99m}Tc in adults and children. As a worst case estimate we assume that the volume of the eluate from the ^{195m}Au generator is not reduced for children, and that the maximum breakthrough dose of 120 kBq ^{195m}Hg is injected. The comparisons are made with ^{99m}Tc activities reduced according to body weight. Body weight factors were taken from Administration of Radioactive Substances Advisory Committee guidelines (appendix 1B).¹³

Discussion

For some years, radionuclide angiographic techniques have proved useful in the assessment of patients with left to right intracardiac shunts.^{1-3,6} The technique has been validated against oximetry and has proved valuable in the investigation of congenital heart disease in children.^{4,5} The radionuclide most widely used for shunt evaluation is ^{99m}Tc, which has a relatively long half life of six hours. ^{195m}Au, has a half life of 30.5 seconds and is available in generator systems⁷ from a ^{195m}Hg parent (half life 41.6 hours). The physical characteristics of ^{195m}Au ensure that the patient is subjected to minimal radiation dose. With all mercury-195m/gold-195m generators, however, the eluate is contaminated by ^{195m}Hg breakthrough. In our generator system the mean ^{195m}Hg breakthrough dose was 96 kBq per injection, with a maximum of 120 kBq. Mena *et al.*, using a different type of generator, quote a figure of 0.75 kBq ^{195m}Hg/^{195m}Au,¹⁴ implying a dose of 550 kBq of ^{195m}Hg per injection of 740 MBq of ^{195m}Au.

Because mercury accumulates in the kidneys radi-

Table 3 Whole body effective dose equivalents of radionuclides in adults and children calculated with weighting factors from Administration of Radioactive Substances Advisory Committee appendix 1B¹³

Age	^{195m} Au + ^{195m} Hg (5 injections)		^{99m} Tc (1 injection)	
	μSv	mrem	μSv	mrem
Adult	430	43	4120	412
10 years	860	86	4120	412
5 years	1400	140	4120	412
1 year	2580	258	4120	412
Newborn	7230	723	4120	412

ation doses from the breakthrough of $^{195\text{m}}\text{Hg}$ are important. But even in the case of a 1 year old child, the effective whole body dose equivalent from five $^{195\text{m}}\text{Au}$ studies is less than that from a single $^{99\text{m}}\text{Tc}$ study (Table 3). The dose to the kidneys of a 1 year old child when $^{195\text{m}}\text{Au}$ is used would be 12 mSv (1200 mrem), which, although it is high, is the same as the dose to the upper large intestine when 370 MBq $^{99\text{m}}\text{Tc}$ is given. In the newborn infant, kidney doses could be as high as 34 mSv (3400 mrem) if five studies are performed. In this study, however, multiple injections were given only to older children and adults and no child under the age of 6 years was studied. In routine clinical practice it is unlikely that more than two studies would be performed, and this would reduce the worse case estimates quoted here. We conclude that the radiation doses from eluates obtained from the type of $^{195\text{m}}\text{Au}$ generator used in this study are acceptable in all except the very young infant. Further, compared with existing techniques a significant reduction in radiation dose can be achieved in most patients, even when several $^{195\text{m}}\text{Au}$ studies are performed.

The $^{195\text{m}}\text{Au}$ is eluted immediately before use and an eluate may be collected sufficiently rapidly for repeat studies to be performed after an interval as short as 2 minutes.¹⁵

We compared the results of the $^{195\text{m}}\text{Au}$ studies with those obtained by a $^{99\text{m}}\text{Tc}$ technique that was validated against oximetry. We also assessed the effects of intervention on the results obtained. There was excellent agreement between the results obtained by the $^{195\text{m}}\text{Au}$ and $^{99\text{m}}\text{Tc}$ techniques (Fig. 4), and all five patients in whom the ratio (Qp:Qs) was calculated to be >3:1 with $^{99\text{m}}\text{Tc}$ had similar flow ratios calculated with $^{195\text{m}}\text{Au}$. The two successive $^{195\text{m}}\text{Au}$ studies without intervention also accorded well, demonstrating the reproducibility of the technique. These results confirm those of Treves *et al* who were able to quantify shunts with iridium-191m,¹⁶ another radionuclide with a short half life. They did not, however, perform sequential studies, and the very short half life of the $^{191\text{m}}\text{Ir}$ (4.96 s) and its relatively low energy, mean that it is less suitable for imaging than $^{195\text{m}}\text{Au}$.

The administration of oxygen might be expected to increase the ratio of pulmonary flow to systemic flow as a result of pulmonary artery vasodilatation, assuming that the pulmonary vascular bed is reactive. Fujil *et al* suggest that patients with high flow ratios have retained such reactivity, whereas in those with lower values the resistance is fixed.¹⁷ Unlike the eight patients studied by Fujil *et al* none of our patients with Qp:Qs values between 2 and 3:1 had end stage disease or Down's syndrome (6/8 in Fujil's study). There was little change in the ratio of pul-

monary flow to systemic flow after oxygen administration in our study, suggesting either that a longer period of administration was needed to change the flow ratio in this group, or that ratios did not change sufficiently to reflect alterations in pulmonary vascular reactivity. The latter assumption is supported by the lack of change on straight leg raising, an intervention which would be expected to cause a fall in ratio as a result of systemic vasodilatation.

The values obtained in the left anterior oblique view were no different from those obtained in the anterior view. We had hoped to identify the site of shunting in this projection but were unable to do so. The left anterior oblique projection is, therefore, of little use because it is more awkward to achieve than the anterior view and does not provide additional information.

In this study we applied a recirculation correction if we could identify a good recirculation curve.¹⁸ In most cases this correction was not essential, but occasionally it made fitting of the secondary curve easier. We found that use of intravenous cannula allowed excellent flushing of the bolus by saline without leakage and in only one case was it impossible to calculate the ratio of pulmonary flow to systemic flow. In this instance the bolus had become fragmented and even deconvolution of the curve would have proved fruitless.¹⁹

In summary, quantification of intracardiac shunts by means of the radionuclide $^{195\text{m}}\text{Au}$ is reproducible and accurate. The results are not affected by oxygen, exercise, or the choice of projection and the low radiation dose makes the radionuclide suitable for use in children with suspected left to right shunts. The combination of this technique with cross sectional echocardiography may obviate the need for cardiac catheterisation in children with simple congenital defects.

We thank Mr Laurence Freedman for his help with the statistical analysis and Mrs Christine Taylor for her help in the programme of the studies. We also thank the Atomic Energy Research Establishment, Harwell for the supply of the generators.

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Mitral valve prolapse, aortic compliance, and skin collagen in joint hypermobility syndrome

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SUMMARY Mitral valve prolapse was sought clinically and with phonocardiography and M mode and sector echocardiography in 15 women aged 22-57 years with joint hypermobility syndrome. The type III:III + I collagen ratio was measured in skin biopsy specimens and was found to be raised in seven of 10 patients sampled. Thirteen patients had increased aortic wall compliance measured by the continuous wave Doppler ultrasound technique. Ten (67%) patients had mitral valve prolapse shown by auscultatory signs or echocardiography or both—a prevalence at least three times greater than that in the general adult population.

It is concluded that if the abnormality of collagen biosynthesis found in skin biopsy samples in these patients is also present in their mitral valve tissue this may predispose them to prolapse of the valve.

The primary mitral valve prolapse syndrome is one of the commonest cardiac abnormalities, being present in 4-21% of the adult population.¹² Most of those affected are symptom free and have a good prognosis,³ but sudden death,⁴⁵ infective endocarditis,⁶ spontaneous chordal rupture, and progressive mitral regurgitation⁷ are rare complications and make this an important condition to recognise. The subject has been well reviewed.²⁸⁻³²

The synonymous term, floppy mitral valve syndrome, emphasises the well established structural abnormality of the valve leaflets, although the molecular basis for this defect remains unclear. The main structural abnormality of the valve leaflets in primary mitral valve prolapse consists of myxomatous degeneration and disruption of the pars fibrosa and there is dilatation of the mitral annulus.²¹²

The association of mitral valve prolapse with certain inherited diseases (secondary mitral valve prolapse) including the Marfan syndrome,¹³ the Ehlers-Danlos syndrome,¹⁴ and osteogenesis imperfecta,¹⁵ lends support to the hypothesis that mitral valve prolapse may be due to abnormalities in the

production or structure of collagen. Such changes have been shown to occur in these conditions.¹⁶

The hypermobility syndrome is a sex influenced usually dominantly inherited disorder of collagen production characterised by non-inflammatory joint pain associated with generalised joint laxity.¹⁷ Mitral valve prolapse is present in about a third of cases,¹⁸¹⁹ providing further evidence that a systemic abnormality of collagen may be associated with mitral valve prolapse. There is, at present, little information on this connection. One study of the family of a patient with type IV Ehlers-Danlos syndrome has shown a consistent association of mitral valve prolapse and abnormally low type III collagen production.²⁰ A more recent study, however, has shown an increased proportion of type III collagen in floppy mitral valve tissue compared with normal controls.²¹

The purpose of this study, therefore, was to assess the frequency of mitral valve prolapse among a group of patients who had evidence of a generalised connective tissue disorder and examine the link with the ratio of III:III + I collagen types in skin biopsy specimens.

Patients and methods

Fifteen patients (all female, with an age range of 22-57, mean 39 years) were selected from a group of

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Accepted for publication 22 July 1985

72 consecutive patients (62 women, 10 men) with joint hypermobility and joint pain attending Guy's Hospital rheumatology department. Radiographs of the affected joints were normal, and all patients were seronegative.

These 15 patients were selected because they had clinical evidence of generalised connective tissue weakness. Eleven of the 15 patients had skeletal signs (arm span 3 inches (7.62 cm) greater than height, scoliosis, pectus excavatum, high palate, antimongoloid slant to the eyes, long fingers). Eight had dermatological signs (thin, hyperextensible skin, striae, easy bruisability), and eight had eye signs (hypertelorism, epicanthic folds, redundant upper eyelids, severe myopia, strabismus). In addition, a clear family history of joint hypermobility associated with pain in a first degree relative, most often a mother or sister, was obtained from all but one patient (case 4).

JOINT HYPERMOBILITY

All the patients were examined by one of us (AHC), and joint mobility was graded by the hypermobility score of Beighton and Horan.²² The scoring system is as follows: (a) passive hyperextension of the fifth metacarpophalangeal joint to 90° scores 1 for each hand; (b) passive apposition of the thumb to the volar aspect of the forearm scores 1 for each thumb; (c) passive hyperextension of the elbow to more than 10° scores 1 for each arm; (d) passive hyperextension of the knees to beyond 10° scores 1 for each leg; (e) placing hands flat on floor by flexing spine while maintaining knees straight scores 1. The maximum score is 9. A score of ≥ 3 indicates a widespread hypermobility of the joints.

COLLAGEN III:III+I RATIO ASSESSMENT

Collagen types I and III were measured by a modification of the method described by Light.²³ After local spray anaesthesia, small, full thickness, scissor biopsy specimens of forearm skin tissue were taken and frozen immediately at -70°C and then dissolved in formic acid. Collagen types I and III were measured by sodium dodecyl sulphate polyacrylamide gel electrophoresis after digestion of skin samples with cyanogen bromide.

AORTIC WALL COMPLIANCE

Collagen comprises nearly half of the content of the aortic media and makes the greatest contribution to the tensile strength of the wall. The distensibility of the aortic wall is measurable by Doppler shift continuous wave ultrasound signals²⁴ and is directly related to vessel compliance. This is defined as the fractional distension of diastolic lumen diameter per

unit of pulse pressure: $C = (\Delta D/D)/\Delta P$, where C is the vessel compliance and ΔD is the increase in diameter of the lumen D produced by an increment of pressure P . Compliance is usually expressed as $C\%$ per 10 mm Hg change in pulse pressure. Thus the distensibility of the aortic wall, which depends on its tensile strength, is directly related to the vessel's compliance.

The optimum method for measuring aortic compliance requires a system that is capable of measuring the change in luminal diameter produced by changes in pressure along the full length of the aorta. This takes into account variation in collagen content of the aortic wall and variable aortic tethering.

Accurate measurement of aortic pressures is not easily obtained except by direct aortic catheterisation. Pulsed wave echo ultrasonography allows the measurement of aortic compliance at given sites but not along the aortic length.

Aortic compliance cannot be measured directly by the continuous wave Doppler technique but it is possible to measure the characteristic pulse wave velocity by recording Doppler shift signals generated by reflection of the ultrasound beam from passing red blood cells at two simultaneously insonated sites on the aortic pathway. The pulse wave velocity (PWV) equals L/T ; where L is the distance between the two sites, T the delay time for the same heart beat at sites L apart between the start of systolic upswing of the blood velocity Doppler shift pulses.

The characteristic pulse wave velocity is dependent on the blood density and the elastic modulus of volume distensibility of the artery wall per unit length.²⁴ The variability and reproducibility of this method have been studied in 900 normal volunteers.²⁵ Normal values for aortic compliance are low in the neonate, rise gradually to a peak at 10 years of age, and then fall gradually to adult levels. These studies have shown that the maximum standard deviation from the mean in each cohort is 10% and that there is no appreciable variation in aortic compliance with blood pressure changes within physiological limits.²⁵ The normal range is taken as 100 (2 SD) (that is 80–120%) (Fig. 1).

Aortic compliance is not corrected for blood pressure as there is little variation in aortic compliance with change in blood pressure at physiological pressures.²⁵ It has also been shown that the maximum variability of aortic compliance throughout the day is 9.1%. Hourly aortic compliance was measured during the day in six symptom free adults (four men, two women, aged 20–26 years) who continued their usual daily activities (S Kontis, personal communication). Only variations $>10\%$ were regarded as abnormal in this study—that is values above 130% or below 70%.

Table Summary of results and clinical data

Patient	Age (yr)	Joint hypermobility (max = 9)	Aortic compliance (%)	Collagen III:III + I	Cardiography				Symptoms
					Echo	Phono	Auscultation	ECG	
1	22	8	100	27	MVP	MSC	MSC	N	Palpitation
2	27	3	167	24	MVP	MSC	MSC	N	Dyspnoea
3	28	5	145	27	N	N	N	N	—
4	29	6	138	—	N	N	N	N	—
5	31	2	118	28	N	N	N	N	ACP
6	31	5	157	25	N	N	N	N	—
7	33	5	130	29	MVP	N	N	N	—
8	38	1	148	—	MVP	MSC	MSC	N	—
9	44	5	144	30	N	MSC	MSC	T inv, II, III, aVF	Palpitation
10	45	5	141	—	N	N	N	N	—
11	50	1	143	—	MVP	N	N	T inv, VI, III	—
12	52	7	149	—	MVP	MSC	MSC	1st deg HB, T inv, II, III	ACP
13	53	4	139	31	MVP	MSC	MSC	N	Palpitation
14	53	7	169	33	MVP	MSC	N	N	Dyspnoea
15	53	7	217	46	MVP	N	N	N	—

ECG, electrocardiogram; ACP, atypical chest pain; MVP, mitral valve prolapse; MSC, midsystolic click; HB, heart block; T inv, T wave inversion
 Aortic compliance: normal range 80–120%, mean 145% in these patients.
 Collagen III:III + I normal range 23–27%, mean 30% in these patients

METHOD OF MEASURING AORTIC COMPLIANCE

The pulse wave velocity was measured with the patient supine and unsedated. A hand held probe from a 4 MHz bidirectional Doppler ultrasound velocimeter (Sonicaid, Vasoflow 2 BV 980) was placed in the left supraclavicular fossa over the subclavian artery, pointing medially. Simultaneously, a probe from an identical 4 MHz bi-directional Doppler ultrasound velocimeter was placed over the abdominal aorta at the level of the umbilicus, just proximal to the aortoiliac bifurcation. The instantaneous spectrum of blood velocities in the vessel lumen at each site was monitored by recording the Doppler shift in frequency of the backscattered ultrasound signals on to stereomagnetic tape. The Doppler ultrasound velocimeters were modified by means of frequency domain processing to display both forward and reverse flow on each channel. The distance (L) was taken from the midpoint on the medial side of the sternal notch to the transducer site on the abdomen. From cadaver studies this has been shown to be within 5% of the effective aortic pathway.²⁶ Brachial blood pressure was recorded at the end of the measurement.

The recorded audio frequency Doppler shift signals from the two sites were simultaneously spectrally analysed on separate channels of a spectrum analyser (Doptek). A hard copy printout of the resultant sonogram on ultraviolet light sensitive paper (Kodak Linagraph 1801) was obtained by means of a fibreoptic recorder (Medilec SOR 1002). The delay

time (T) between the start of the systolic velocity upstroke for each pulse was measured with an electronic digitiser (Summagraphics, Bitpad) and a microcomputer (Commodore Pet type 8032). Care was taken to obtain the value of T from the systolic foot to foot separation of the proximal and distal waveforms, and T was averaged for at least 20 pulses to minimise change in the aortic compliance caused by pressure fluctuations with respiration. Aortic compliance was then calculated from the equation:

$$C\% \text{ per } 10 \text{ mm Hg } (1.33 \text{ kPa}) = 66.7 (T/L)$$

Aortic compliance (C) was expressed as a percentage of the normal value found per 10 mm Hg change in pulse pressure.²⁴

CARDIAC ASSESSMENT

All the patients were examined by one of us (CEH). Auscultatory signs of mitral valve prolapse were sought with patients being examined supine, in the left lateral position, and standing. This was supplemented by a phonocardiographic examination with a Smith Kline Instruments diagnostic module P/N 8544-9000, which was performed with the patient in the 40° left lateral position and breathing gently.

A standard 12 lead electrocardiogram was obtained in all patients. M mode and sector echocardiography were performed by a standardised technique with the patient in the partial left lateral position. We used an Ekoline sector 2 (Smith Kline Instruments) with a 2.1 MHz 90° transducer.

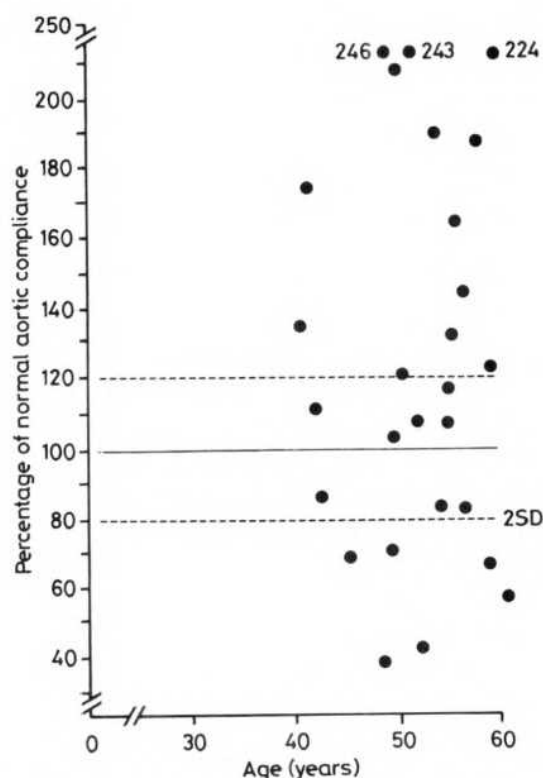


Fig. 1 Aortic compliance (%) of individual subjects plotted against age (years). Mean (solid line) and 2 SD (broken lines) for aortic compliance previously measured in normal subjects are shown.

The M mode echocardiographic diagnosis of mitral valve prolapse was made by showing mid to late systolic displacement of one or both leaflets at least 2 mm below the line joining the point of valve closure in systole (C) to the point of valve opening in diastole (D); or a pansystolic posterior displacement of at least 3 mm below the line joining C and D with the least displacement occurring in mid systole.²⁷ The criterion for diagnosis of mitral valve prolapse on the sector scan was protrusion of a portion of one or both mitral valve leaflets across the plane of the atrioventricular ring into the left atrium during systole.^{28,29} Mitral valve prolapse was diagnosed if either the M mode or sector scan echocardiographic criteria were fulfilled.

Results

The Table summarises the results and clinical data.

AORTIC COMPLIANCE

Thirteen of the 15 patients had a significantly increased aortic compliance (Table). The two highest values were found in the oldest patients, whereas the

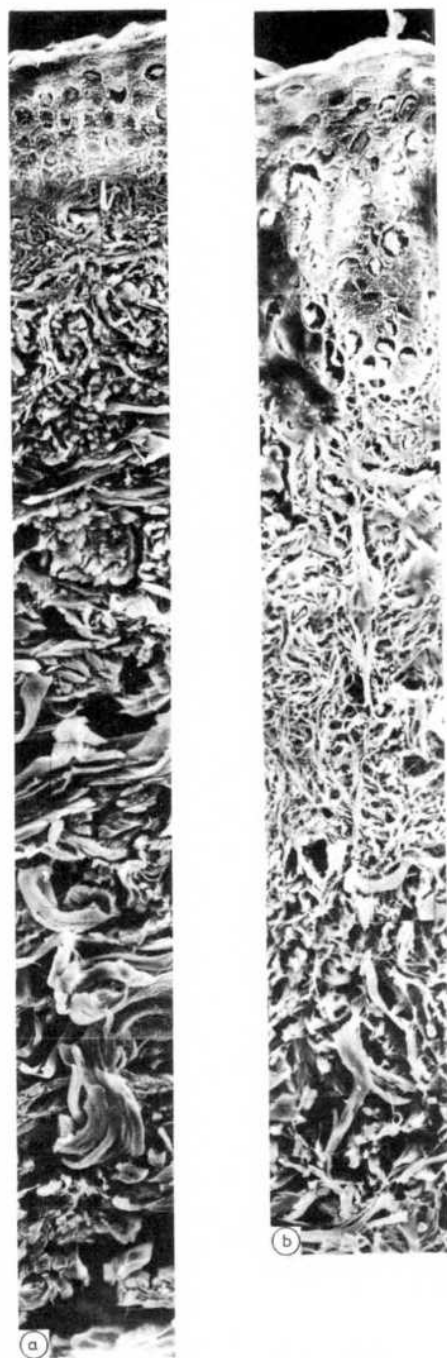


Fig. 2 Scanning electron micrograph of a skin biopsy specimen from an age and sex matched control (a) and a patient (b) (case 13) with mitral valve prolapse, raised collagen type III:III + I ratio in the skin, and increased aortic compliance. Case 13 had decreased skin thickness, a decreased proportion of thick collagen fibres, and an increased proportion of fine disorganised collagen fibres.

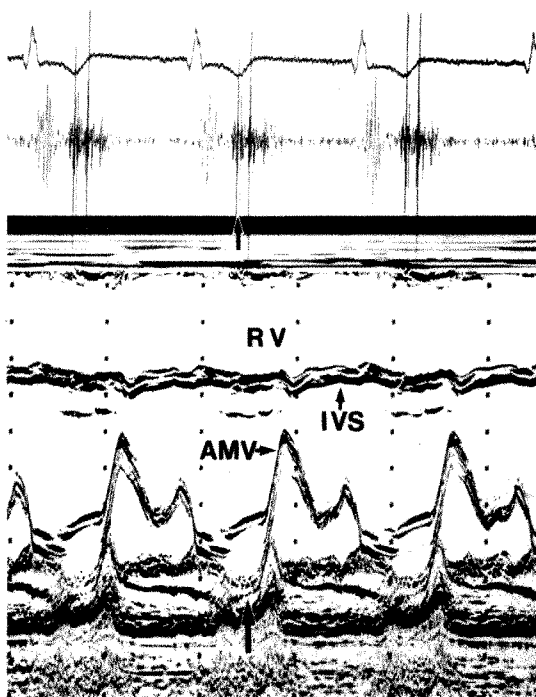


Fig. 3 Surface electrocardiogram (top), phonocardiogram (middle), and M mode echocardiogram (bottom) from a patient (case 12) who had clinical, echocardiographic, and phonocardiographic features of mitral valve prolapse and T wave inversion and first degree heart block (PR interval 0.24 s) on a resting 12 lead electrocardiogram. Lower arrow indicates prolapse of the posterior mitral valve leaflet. RV, right ventricle; IVS, intraventricular septum; AMV, anterior mitral valve leaflet.

youngest patient had a normal value. There was no significant correlation of aortic compliance either with age or with skin collagen type III or types III+I.

SKIN COLLAGEN III:III+I RATIO

In six of the 10 patients sampled the ratio of III:III+I collagen in the skin was increased. In the three patients aged more than 53 years these ratios were 31%, 33%, and 46%. Samples from the three youngest patients (aged under 28 years) were within normal limits. Skin collagen ratio III:III+I increased significantly with increasing age ($p < 0.01$).

Fig. 2 shows a typical scanning electron micrograph of a skin biopsy specimen from a patient (case 13) with mitral valve prolapse, raised type III:III+I collagen ratio in the skin, and increased aortic compliance, compared with a skin biopsy specimen from a normal age and sex matched control. The micrograph of case 13 shows decreased

skin thickness, a decreased proportion of thick collagen fibres, and an increased proportion of fine disorganised collagen fibres.

CARDIAC FINDINGS

Five patients had both auscultatory and echocardiographic features typical of mitral valve prolapse. One patient had a mid systolic click on phonocardiography and mitral valve prolapse on echocardiography but no abnormality detected by auscultation. One patient had a click on phonocardiography and on auscultation but had a normal echocardiogram. Three patients had mitral valve prolapse diagnosed only by echocardiography. Thus 10 of the 15 patients had mitral valve prolapse diagnosed by one or more of the criteria used and in nine of these patients echocardiography was positive. Fig. 3 shows a representative M mode echocardiogram (from case 1).

Three patients had an abnormal electrocardiogram, and all three had mitral valve prolapse. The electrocardiographic abnormalities consisted of non-specific T wave inversion in the inferior leads and, in one patient, first degree heart block. Seven patients had cardiac symptoms (mainly palpitation and atypical chest pain), and one of these did not have mitral valve prolapse. Three patients with echocardiographic evidence of mitral valve prolapse were symptom free.

Discussion

Our findings are consistent with those from other studies in which an increased frequency of secondary mitral valve prolapse has been found in patients with certain connective tissue diseases¹²⁻¹⁶ and an abnormality of collagen. The results also suggest that a raised generalised ratio of collagen types III:III+I may be important in the pathogenesis of this condition, which has been attributed to a disorganisation of the lamina fibrosa of the mitral valve cusps.³⁰

Our results accord with those of a recent study by Cole *et al* on normal and floppy valves from necropsy and surgical material.²¹ They found a greatly increased amount of type III collagen and a smaller increase in type I collagen in tissue from the floppy valve.

Evidence for the heterogeneity of collagen deficiency in this condition has come from Hammer *et al*, who reported a deficiency of types III and V collagen in a floppy mitral valve.³¹

An earlier study by Jaffe *et al* on the family of a proband with classic type IV Ehlers-Danlos syndrome also provides evidence for an abnormality of type III collagen production in patients with co-

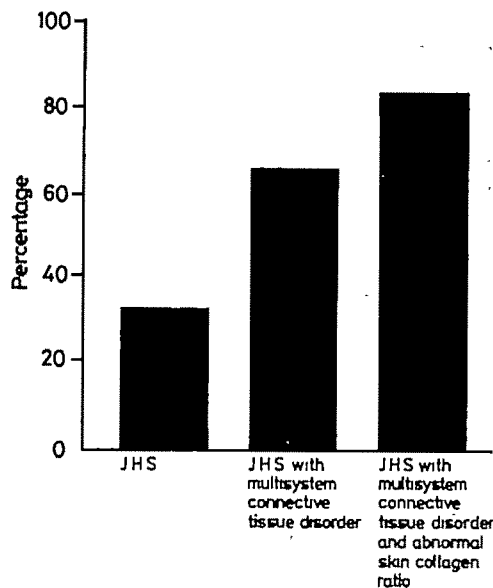


Fig. 4 Histogram showing the prevalence of mitral valve prolapse (%) reported in joint hypermobility syndrome (JHS),¹⁸ in joint hypermobility syndrome with additional evidence of connective tissue disorder,¹⁹ and the frequency found in the present study. The frequency of mitral valve prolapse in patients with joint hypermobility, multisystem connective tissue disorder, and abnormal skin collagen is at least three times that in the general adult female population.

existing mitral valve prolapse.²⁰ They found a lower type III collagen production in those patients with mitral valve prolapse than in family members who did not have mitral valve prolapse. An increased prevalence of mitral valve prolapse has been found in patients with osteogenesis imperfecta,¹⁵ where collagen type I is abnormal. These reports and our own data strongly suggest heterogeneous abnormalities of collagen biosynthesis in patients with mitral valve prolapse.

SKIN COLLAGEN RATIOS

Skin collagen ratios were measured in only 10 of our 15 patients. When we were establishing the microassay used in this study, the collagen extracts from four age matched controls and patients 4, 8, 10, 11, and 12 were run on a gel and the results were technically unsatisfactory. This is a clear disadvantage of working with small samples as there may not be enough collagen peptides to repeat a run. These five patients could not undergo repeat biopsy because they had been entered into a drug trial which affected their skin collagen ratios. In a previous study, however, the ratio of collagen types III:III+I in abdominal skin from normal donors ranging in age from 3 months to 92 years was shown to be 18–21%

for young and middle aged donors.³² In older donors the relative amount of type III collagen was increased to varying degrees (24–28%). In the present study six patients had increased ratios of type III:III+I (28–40%) compared with four normal age and sex matched controls in whom values ranged from 24% to 26%. In two patients aged 53 years these ratios were above 30% and in one (aged 57) it was 46%. These values reflect extreme abnormalities in collagen metabolism in the skin.

All of our patients were selected because they had joint hypermobility, which mainly affects females.¹⁸ Both joint hypermobility syndrome and mitral valve prolapse are inherited as sex influenced dominant traits and predominantly affect women.³³ Since all of our patients were females, we cannot draw firm conclusions about the relevance of our findings to male patients with primary or secondary mitral valve prolapse. Further studies are required to clarify this point.

AORTIC COMPLIANCE

Most of our patients had a raised aortic compliance indicating an increased distensibility of the aortic wall. This is presumably related to abnormal collagen in the media. Abnormally high values for aortic compliance have been reported in various inherited connective tissue disorders including those with a known collagen abnormality.³⁴ The raised values in our patients confirm the presence of a generalised connective tissue disorder.

The normal aortic compliance in the youngest patient may reflect the variability of expression of the gene determining this disease, producing lax ligaments and joint capsules while leaving the aorta relatively unaffected. It would be interesting to re-measure the compliance in this patient at a later date to assess whether her mitral valve prolapse has progressed.

In a previous blind study the aortic compliance of nine patients with Ehlers-Danlos syndrome type IV was found to be significantly increased.³⁵ The more severely affected patients with very low type III collagen production had the highest compliance values. In a second blind study aortic compliance was shown to be increased in six out of 10 patients with ruptured intracranial aneurysm.³⁶ Four of the six patients had low production of type III collagen in skin fibroblasts.

Joint hypermobility syndrome, in which there is an apparent deficiency of collagen type I with overproduction of collagen type III, is a third instance of a collagen deficiency disease in which structural cardiovascular weakness (here of the mitral valve) is associated with increased aortic compliance.

CARDIAC FINDINGS

One of our patients (case 9) had auscultatory and phonocardiographic signs of mitral valve prolapse and a normal M mode and sector echocardiogram. Most investigators have found that about 10% of patients with typical auscultatory findings do not have prolapse on echocardiography and vice versa.² This weak association between physical signs and echocardiographic features of mitral valve prolapse is corroborated by the Framingham study.³⁷ It is also conceivable that one or more of our patients had echonegative and silent mitral valve prolapse. None of our patients had murmurs, and this is perhaps a little surprising since soft systolic murmurs may be present in apparently healthy women.³⁸

Certain electrocardiographic abnormalities, including non-specific T wave changes, are well recognised in patients with mitral valve prolapse.^{10,39} All three patients with abnormal electrocardiograms in this study had mitral valve prolapse.

Sudden unexpected death is a rare but recognised complication of secondary mitral valve prolapse. Recently, Pocock *et al* reported a young patient with mitral valve prolapse who died suddenly.⁴⁰ They suggested that she had ventricular fibrillation which was probably related to multifocal premature ventricular contractions. They have assembled sixteen other cases of sudden death in patients with mitral valve prolapse, and although they emphasise that the frequency of sudden death is low, they stress the importance of identifying the small group of patients at higher risk and of managing them appropriately.

Because the risks of sudden death and other complications, including those requiring valve replacement, appear small, physicians usually reassure most patients who have only echocardiographic evidence of mitral valve prolapse but may keep them under periodic review. Antibiotic prophylaxis against infective endocarditis is, at present, usually recommended only for those patients who have systolic murmurs,⁴¹ but this approach is not universal. The results from this study suggest that all patients with hypermobility syndrome and signs of generalised connective tissue deficiency should have careful clinical assessment with echocardiography because the frequency of mitral valve prolapse is likely to be high (Fig. 4). Antibiotic prophylaxis should be seriously considered in patients shown to have mitral valve prolapse, since endocarditis can develop (albeit rarely) in patients who have clicks and no murmurs.^{41,42}

It is not yet known whether those patients in whom complications develop are more likely to have a generalised connective tissue disorder and a more severely abnormal mitral valve structure or both than those with a good prognosis.

The results of our study suggest a link between secondary mitral valve prolapse and abnormal skin collagen. It would be of interest and possible clinical importance to assess collagen characteristics in mitral valve tissue from patients with hypermobility syndromes and also to assess collagen characteristics in skin and, whenever possible, mitral valve tissue from patients with primary mitral valve prolapse. If there is a common abnormality of collagen in the skin and mitral valve tissue, then it is possible that this could be of relevance in those patients who develop progressive mitral regurgitation or abrupt severe mitral regurgitation due to chordal rupture.

We thank Dr Mary Dyson, Department of Anatomy, Guy's Hospital, for interpreting the electron-micrographs of the skin and Dr Rodney Grahame, Department of Rheumatology, Guy's Hospital, for allowing us to study his patients.

CEH was supported by the Medical Research Council, AC was supported by the British Heart Foundation, the Arthritis and Rheumatism Council, and Corda, and DED was supported by the South East Thames Research Committee.

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Exercise radionuclide ventriculography in children: normal values for exercise variables and right and left ventricular function

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SUMMARY Thirty two children (aged 5-19 years) with no clinical evidence of significant cardiovascular disease undertook continuous staged supine exercise on a bicycle ergometer. Multigated radionuclide ventriculography was performed at rest and during each exercise stage. Exercise duration and total workload both increased with age. Aerobic work correlated better with age than did total work. In most children the ejection fraction for both ventricles increased by at least 5% with exercise. Right ventricular ejection fraction did not decrease with exercise in any subject but left ventricular ejection fraction decreased by 2% and 9% in two. The response of end diastolic volume to exercise was variable, but there was a consistent decrease in mean (SD) end systolic volume of the left (29(22)%) and right (30(19)%) ventricles. Cardiac index (mean (SD)) increased by 234(65)% with exercise. The left ventricular:right ventricular end diastolic volume ratio (mean (SD)) at rest was 1.26(0.26).

It is concluded that exercise radionuclide ventriculography is an excellent technique for a combined assessment of exercise capacity and an evaluation of ventricular size and performance in children. These values for supine bicycle exercise in children without significant cardiovascular disease will be useful for future comparisons with other groups.

Abnormalities of ventricular performance have been reported in children with diverse types of heart disease.¹⁻³ In several studies radionuclide ventriculography and exercise stress testing were used to assess such children.⁴⁻⁶ Most of these studies, however, have compared results from "abnormal" children with published data on normal adults. No data are available on the results of exercise radionuclide ventriculography in normal children, nor are data available on normal workloads, heart rate, and blood pressure response to supine bicycle exercise with a 4 minute per stage graded exercise protocol. We report the results of radionuclide ventriculography in 32 children who undertook supine exercise on a bicycle ergometer.

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Patients and methods

STUDY GROUP

Between June 1980 and June 1983 we performed radionuclide ventriculography in 220 children. All had been referred for investigation for clinical reasons, and informed consent was obtained from each patient and their parents (institutional review committee approval, July 1982). Patients were eligible for inclusion if they had undergone an exercise radionuclide ventriculogram and they had no clinical evidence of structural heart disease, cardiac dysfunction, or congestive heart failure; were taking no medications; had no history of exercise intolerance; and had a normal baseline electrocardiogram, chest x ray film, and echocardiogram. Thirty two of our 220 patients met these criteria. These 32 patients ranged in age from 5 to 19 years (mean (SD) 12.4(3.6) years). Their weights ranged from 15 to 60 kg (mean (SD) 44.3(17) kg).

Ethical considerations prevent the recruitment of healthy children solely for the purposes of a radionuclide study. The diagnoses with which our 32 patients were referred were as follows; arrhythmias (extrasystoles or paroxysmal atrial arrhythmias) 13 patients; chest pain, seven patients; postoperative state, seven patients (six patients had had atrial septal defect repair and one patient had had repair of a partial anomalous pulmonary venous drainage); pectus excavatum, three patients; hyperlipidaemia, one patient; and normal heart, one patient. All postoperative patients had been operated on before the aged of 6 and were studied at least a year after operation. All patients (including those with a history of arrhythmias) were in normal sinus rhythm at the time of radionuclide study and did not have a history of chronic or incessant tachycardia. There was therefore no clinical reason to suspect any abnormality of ventricular function in these children.

Initially, results for the postoperative patients were examined separately and compared with the remaining patients. Since no significant differences were found all patients were subsequently grouped and analysed together.

EXERCISE PROTOCOL

The patients performed supine exercise on a bicycle ergometer and followed a continuous staged protocol similar to that described by Godfrey.⁷ Exercise was performed in 4 minute stages with an increase in workload at each stage up to the point of maximum voluntary patient effort. Stages lasting 4 minutes rather than 3 minute stages were chosen because the longer time allows us to obtain better quality radionuclide images. The workload was set at 200 kpm/min (33.4W) for stage 1, and increased by 200 kpm/min (33.4W) for each subsequent stage. Pedal speed was maintained at between 60 and 80 rpm for the duration of the exercise. In all children the rea-

son for stopping exercise was leg fatigue. Three electrocardiographic leads were monitored continuously throughout exercise (modified Frank system). We used an automated device to measure blood pressure in the arm every 2 minutes. This device uses acoustic transduction with electrocardiographic gating and signal filtering and has been validated for use in children during exercise.⁸ In eight children, free flowing venous blood samples for the determination of lactic acid were obtained before exercise and 2 minutes after exercise had ceased. In another seven children free flowing venous blood was obtained from an indwelling antecubital cannula every minute during exercise and for 5 minutes after exercise to determine the onset of metabolic acidosis (lactic acidemia).

RADIONUCLIDE STUDIES

Multiple gated equilibrium radionuclide studies were performed with the subject in the supine position at rest and during the final 3 minutes of each exercise stage. We have already described and validated our data acquisition and analysis techniques.⁹⁻¹¹ All studies were analysed to obtain right and left ventricular ejection fractions at rest and during peak exercise. In addition, we used a geometric formula to calculate left ventricular volumes at rest and with exercise. From these volumes and the ejection fraction we estimated the cardiac index at rest and during peak exercise. Using the regional blood counts, we also calculated a left ventricular to right ventricular volume ratio.

We required at least 1 minute of data acquisition during exercise to accumulate adequate radionuclide data. Eleven children exercised for less than 2 minutes (mean (SD) 1.0(0.4) minutes) of their final exercise stage. Thus for these children we used the preceding radionuclide image (obtained during the stage just before maximum exercise) to calculate peak exercise performance indices. The remaining

Table 1 Exercise performance in children aged 5-9 years (group 1), 10-14 years (group 2), and 15-19 years (group 3)

	1	2	3
No patients	7	17	8
Age (yr)	7.3 (1.1)	12.4 (1.5)*	16.9 (1.3)*†
Heart rate (beats/min)	80 (15)	86 (20)	111 (24)*†
Change in systolic blood pressure (mm Hg)	40 (28)	44 (16)	61 (25)
Exercise time (min)			
Boys	8.6 (1.1)	11.6 (2.3)*	17.5 (3.2)*††
Girls	7.0 (0.5)	11.3 (2.9)*	12.2 (2.8)*
Combined	7.9 (1.2)	11.5 (2.4)*	16.1 (3.8)*†
Total work (kpm/m ²)			
Boys	2943 (478)	3546 (901)	5846 (166)*††
Girls	2157 (224)	3458 (1489)*	3444 (932)
Combined	2606 (555)	3515 (1096)	5247 (1829)*†

*Significantly different from group 1, $p < 0.05$.

†Significantly different from group 2, $p < 0.05$.

††Boys significantly different from girls: $p < 0.05$.

Conversion: traditional units to SI—1 kpm/m² = 9.807 J/m².

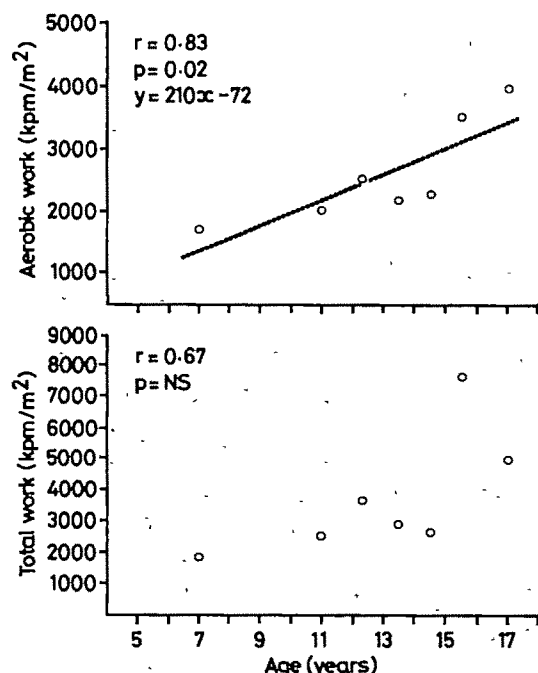


Fig. 1 Work performed on the bicycle ergometer by patient age. See text for explanation of aerobic work. kpm/m^2 , kilopond metres per square metre. Conversion: traditional units to SI— $1 \text{ kpm/m}^2 = 9.807 \text{ J/m}^2$.

21 children exercised for 2–4 minutes (3.3 (0.8) min) of their final exercise stage and had adequate radionuclide images for this last stage.

STATISTICAL ANALYSIS

Group values obtained at rest and during peak exercise are given as means and standard deviation. Group means were compared by one way analysis of variance followed by a Newman-Keuls multiple comparisons test.¹² Correlations were assessed by linear regression analysis. A probability value of $p < 0.05$ was regarded as being statistically significant.

Results

EXERCISE PERFORMANCE

Table 1 summarises some of the exercise performance results. All patients exercised beyond their anaerobic threshold as shown by the onset of tachypnoea in all patients.¹³ In the subgroup of eight patients in whom lactic acid concentrations were measured they increased from 2.0 (0.8) mg/dl (0.22 (0.09) mmol/l) at rest to 5.6 (1.5) mg/dl (0.62 (0.17) mmol/l) after exercise. Lactic acid concentrations increased by from 1 to 5.5 mg/dl (0.11 to

0.61 mmol/l). Serum bicarbonate concentrations fell before the end of exercise in all seven patients in whom venous blood gases were monitored.

Heart rate always increased by at least 55 beats per minute and blood pressure increased by at least 20 mm Hg (systolic).

We divided patients into three groups (group 1, 5–9 years; group 2, 10–14 years; group 3, 15–19 years) to determine the effect of age and sex on exercise variables.

Sex—There were 43%, 35%, and 38% female patients in groups 1, 2, and 3 respectively. We found no significant difference between boys and girls at any age in the responses of heart rate or blood pressure to exercise. In age group 3, however, boys were able to exercise for a significantly longer period and perform a significantly greater amount of work ($p < 0.05$) than girls.

Age—We found no significant difference between age groups 1 and 2 in the heart rate or blood pressure response to exercise. Age group 3, however, had a significantly greater heart rate increase (but not blood pressure increase) than did the younger patients. In addition, the older patients tended to exercise for longer, and perform more work per square metre of surface area. In boys the total workload per square metre correlated with age ($r = 0.57$, $p < 0.05$), but there was no significant correlation between age and workload in girls.

Since total workload is in part dependent on effort and aerobic capacity we assessed the age dependence of the anaerobic threshold as well as the total workload in the subgroup in which venous blood gases were measured. Aerobic work was defined as the work per square metre achieved before there was an abrupt decrease in base deficit (anaerobic threshold). There was a very strong correlation between aerobic work and age ($r = 0.83$, $p < 0.05$). In this subgroup, however, there was no significant correlation between total workload and age (see Fig. 1). Workload achieved in our three age groups was at least 1900 (18.6) (group 1), 2100 (20.6) (group 2), and 2700 (26) (group 3) kpm/m^2 (kJ/m^2) regardless of sex. The expected aerobic workload (kpm/m^2 ; kJ/m^2) is approximately 210 times the patient's age in years.

RADIONUCLIDE VENTRICULOGRAPHY

Cardiac performance

The ejection fractions of the left and right ventricles are shown in Fig. 2. Only one patient had a resting left ventricular ejection fraction of less than 50%. In this patient, who was referred because of occasional extrasystoles, the left ventricular ejection fraction increased to 70% with exercise. Five patients had resting right ventricular ejection fractions of less than 40%. Three of these patients were being

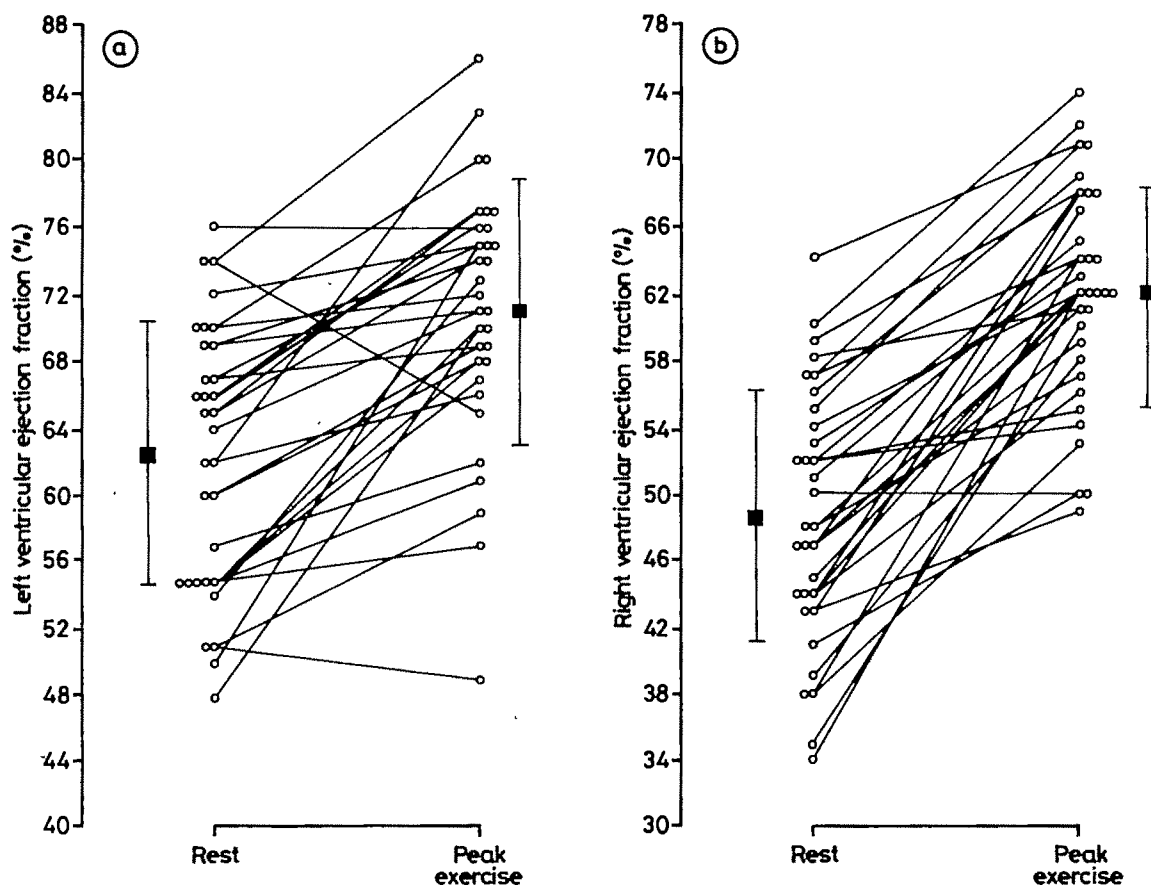


Fig. 2 (a) Left and (b) right ventricular ejection fractions at rest and at peak exercise. Means (1 SD) are given.

investigated for minor arrhythmias, one for chest pain, and one had had repair of an atrial septal defect. In all five patients the ejection fraction increased by at least 5% (5 ejection fraction units) with exercise.

Table 2 summarises the responses of the right and left ventricles to the stress of exercise. Ejection fraction decreased by more than 5% (5 ejection fraction units) in only one patient. This patient had a history of supraventricular tachycardia. Her left ventricular ejection fraction decreased from 74% to 65% with exercise, whereas the right ventricular ejection frac-

tion increased from 45% to 62%.

Nine patients had a change of less than 5% in their left ventricular ejection fraction. In eight of the nine patients their ejection fraction increased slightly (mean $+2.4(0.8)\%$) and in one patient it increased by 2%. Six of these nine patients had a resting ejection fraction of more than 65%. The remaining three patients had resting left ventricular ejection fractions of 62%, 55%, and 51%. The diagnosis at referral in these three patients were paroxysmal supraventricular tachycardia, postoperative atrial septal defect repair, and ventricular ectopy respectively.

Four patients had a change of less than 5% in right ventricular ejection fraction. The ejection fraction increased in all four patients (mean $+2(0.7)\%$). These patients had resting ejection fractions of 58%, 52%, 52%, and 50%. They were referred with hyperlipidaemia, paroxysmal supraventricular tachycardia (2), and chest pain respectively.

Cardiac index increased with exercise in all

Table 2 Ejection fraction changes with exercise (figures are numbers of patients)

	Increase by $>5\%$	Change $\leq 5\%$	Decrease by $>5\%$
Left ventricle	22	9	1
Right ventricle	28	4	0

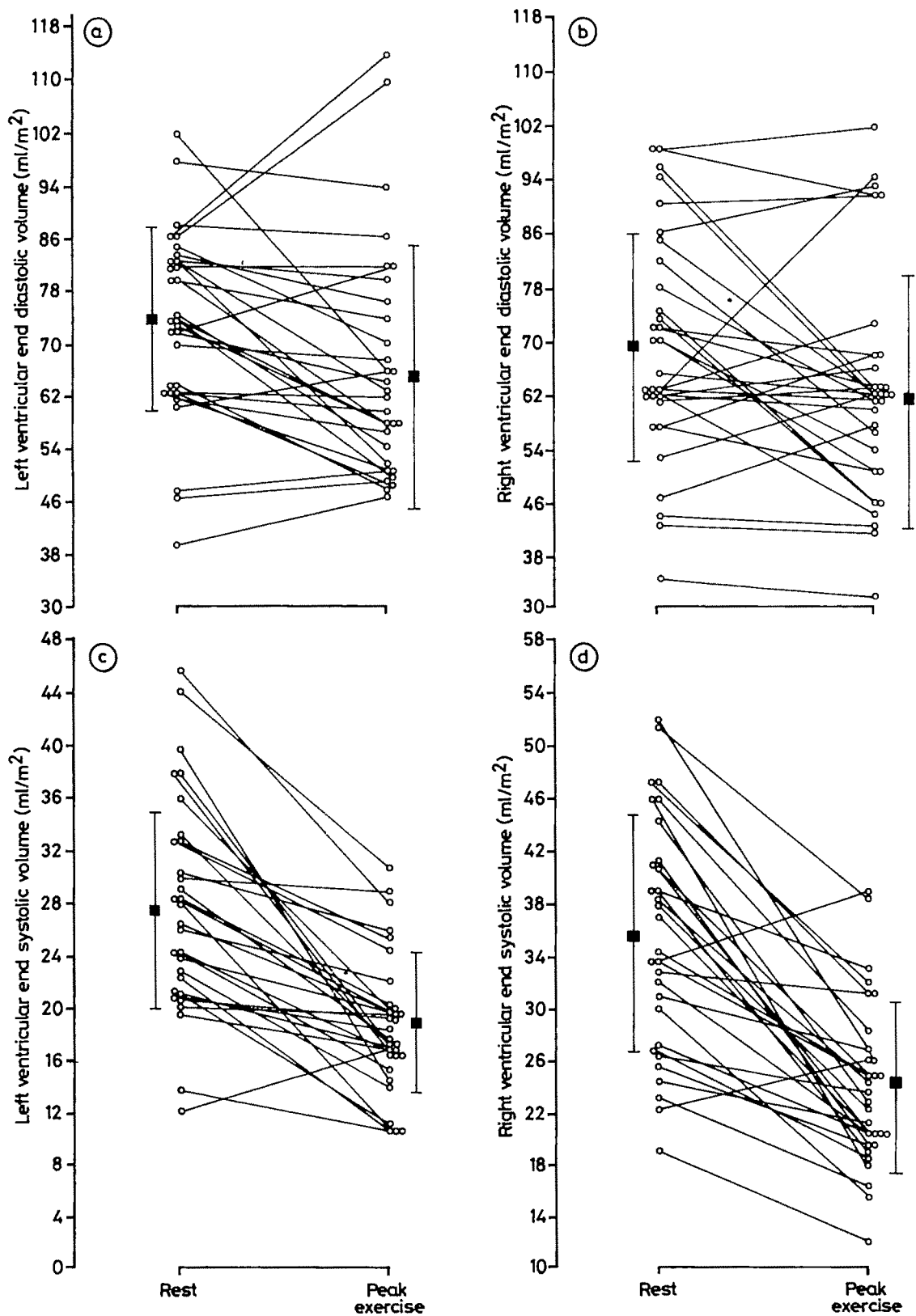


Fig. 3 (a) Left and (b) right ventricular end diastolic volumes and (c) left and (d) right ventricular end systolic volumes determined by a geometric technique at rest and at peak exercise. Means (1 SD) are shown.

Table 3 Results of radionuclide ventriculography in 32 children without significant cardiovascular disease

	Rest		Exercise	
	Lower limit	Upper limit	Lower limit	Upper limit
LV ejection fraction	0.50	0.75	0.55	0.85
RV ejection fraction	0.35	0.65	0.50	0.75
LV:RV end diastolic volume ratio (CT)	0.90	1.85	—	—
LV:RV end diastolic volume ratio (GEO)	0.70	1.50	—	—

CT, method based on regional counts, GEO, method based on geometric volume determination; LV, left ventricle; RV, right ventricle.

patients (+234(65)%). Changes in cardiac index ranged from +129% to +448%. Neither age nor total workload per square metre, however, correlated with change in cardiac index.

Ventricular volumes

Figure 3 shows the ventricular volumes at rest and with exercise. The responses of right and left ventricular end diastolic volumes to exercise were variable. Eight patients showed increases in left ventricular end diastolic volume with exercise, whereas the rest showed a decrease. Similarly, for the right ventricle, 10 patients showed an increase in end diastolic volume and the remaining patients showed a decrease. The mean (SD) change in left and right ventricular end diastolic volumes for the whole group was $-9.8(19.8)\%$ and $-8.1(19.8)\%$ respectively. The differences between the mean resting and mean peak exercise end diastolic volumes were not statistically significant.

The response of the end systolic volumes to exercise was more consistent than that of the end diastolic volumes (Figs. 3c and 3d). All but one patient showed a decrease in left ventricular end systolic volume with exercise. The mean (SD) change for the group was $-29(22)\%$. Similarly, right ventricular end systolic volumes increased with exercise in only two patients. The mean change in right ventricular end systolic volume with exercise was $-30(19)\%$. The peak exercise end systolic volumes of both ventricles were significantly less than their resting end systolic volumes.

One patient in whom left ventricular end systolic volume increased with exercise also showed a 9% decrease in left ventricular ejection fraction. This patient had a history of supraventricular tachycardia but was otherwise normal. In two patients right ventricular end systolic volume increased with exercise. One of these patients (history of supraventricular tachycardia) had an increase in both left and right ventricular ejection fractions with exercise of 6% and 8% respectively. The remaining patient (post-operative atrial septal defect repair) showed an increase of only 4% and 2% for his left and right ventricles respectively.

We also assessed the ratio of the left ventricular

end diastolic counts to right ventricular end diastolic counts. This volume assessment is relatively independent of geometric considerations. As assessed by this count based method the mean (SD) left ventricular to right ventricular end diastolic volume ratio was $1.26(0.26)$ with a range of 0.85 to 1.84. The volume ratio did not change significantly with exercise ($1.28(0.27)$; range 0.93–2.16). A similar volume ratio was derived by geometric estimation of end diastolic volumes. At rest this geometric volume ratio was $1.10(0.22)$ (range 0.70–1.48), and with exercise it was $1.11(0.27)$ (range 0.79–1.77). The difference between the count based and geometric based volume ratios was not statistically significant.

Table 3 summarises what we consider to be normal radionuclide ventriculography findings in children, based on our results in this group of 32 patients without significant cardiovascular disease. The upper and lower limit numbers encompass the range of values seen in our patient group to the nearest 0.05 units.

Discussion

We have already discussed some of the technical considerations when supine exercise and radionuclide ventriculography is performed in children.^{9–11} This technique seems to be safe and the results compare well with cineangiography in children with diverse types of cardiac disease. One potential drawback, however, of the multigated technique used here is that the peak exercise results are an average of cardiac performance for several minutes before the subject stops exercising. Thus, our results at peak exercise may differ slightly from those obtained by other methods which provide a more rapid determination of cardiac performance. The use of a first pass radionuclide technique would avoid this difficulty.^{14–16}

The mean resting right and left ventricular ejection fractions in our study are lower than those usually found by cineangiography^{17,18} or with a first pass radionuclide technique.^{14–16} This may be due to any one of several factors including: inherent differences between a rapid ejection fraction determination (cineangiography) and a time averaging

technique (radionuclide ventriculography); a consistent small error in the correction for background activity; or overlap of atrial and ventricular activity at end systole.

Our results for blood pressure and heart rate response and total work resemble those for upright bicycle exercise in normal children¹⁹ and those for treadmill exercise in normal children.²⁰ In common with these previous studies, we also found that exercise duration and total workload increase with age. In addition, we found that separate analysis of aerobic and anaerobic work by means of venous blood gases seemed to improve our assessment of working capacity by increasing the correlation between age and total workload.

Cardiac output in response to exercise has been measured in normal children by Cumming²¹ and by Lock *et al.*²² They found a mean increase in cardiac output of 187% and 258% respectively. These results resemble the increase of 234(65)% in our study.

The ejection fraction response to exercise for both ventricles has been described in normal adults.²³⁻²⁵ In adults, as in our children, the ejection fraction for both ventricles usually increases by at least 5% (5 ejection fraction units) with exercise. We found that a decrease in right or left ventricular ejection fraction of more than 5% is quite unusual in normal children (1 of 32) and we regard this as an abnormal response. Interpretation of an abnormal ejection fraction response, however, must be cautious because this measure of ventricular performance is influenced by preload, afterload, and contractility.

Relative changes in the end systolic and end diastolic volumes with exercise determine the ejection fraction response to exercise. We found that the right and left ventricular end systolic volumes usually decrease with exercise, whereas the response of the end diastolic volume is variable. Indeed we consider an increase in end systolic volume with exercise to be abnormal since this response is very unusual in normal children. End diastolic volume is more likely to increase during upright exercise.²⁶

We conclude that exercise radionuclide ventriculography is an excellent technique for combined assessment of exercise capacity and evaluation of ventricular size and performance in children.

MDP was supported as a research fellow of the American Heart Association, Tennessee Affiliate.

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Diagnosis and natural history of Ebstein's anomaly

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SUMMARY Thirty five cases of Ebstein's anomaly were diagnosed by cardiac catheter study or echocardiography between 1962 and 1984. The anomaly was an isolated abnormality in 27 patients; the remainder had additional heart lesions. Six patients have died and four of these had other cardiac lesions. Thirteen are currently symptom free. Twelve cases presented with cyanosis and heart murmur on the first day of life. Eight of these had associated thrill which is a rare finding in neonates. As pulmonary vascular resistance fell there was clinical improvement. This was assisted by oxygen treatment. Another two cases presented in the first week of life and 10 in the first decade with a murmur or supraventricular tachycardia. Eleven cases presented as adolescents or adults with a murmur, cardiomegaly, or cardiac symptoms. Three patients were seen initially in the sixth decade. Clinical diagnosis was correct in only one adult.

Twenty five patients had cardiac catheterisation. Important arrhythmias occurred in 10 cases, and two required cardioversion. Difficulty was experienced in entering the pulmonary artery in 11 infants and children. Diagnosis at initial catheter study was incorrect in four patients. Echocardiograms were recorded in 29 cases. Earlier M mode measurements of time delay of tricuspid closure compared with mitral closure did not always lead to the correct diagnosis. Cross sectional studies gave good images of tricuspid leaflet displacement, its tethering, and the atrialised portion of the right ventricle and have facilitated the diagnosis of more cases in recent years. Echocardiography is the procedure of choice for diagnosis of Ebstein's anomaly.

In 1866 Wilhelm Ebstein reported his necropsy findings in a cyanosed 19 year old labourer who had had dyspnoea and palpitation since childhood.^{1,2} The description of a congenital heart abnormality was illustrated by meticulous hand drawings which showed (a) a severe malformation of the tricuspid valve; (b) absence of the valve to the coronary sinus, and; (c) a patent foramen ovale. Several similar cases were described over the next seventy years and the eponym Ebstein's disease was applied to them.^{3,4} It was not until 1949 that a case was diagnosed clinically.⁵

The basic anatomical abnormality consists of displacement of the septal and posterior leaflets of the tricuspid valve from the atrioventricular annulus into the body of the right ventricle. This results in atrialisation of a portion of the right ventricle. The

anterior leaflet is also abnormal and is usually large and sail-like.⁶

We have reviewed the diagnosis and natural history of Ebstein's anomaly in the light of currently available diagnostic techniques.

Patients and methods

All patients in whom Ebstein's anomaly was diagnosed by cardiac catheterisation or echocardiography or both at the Prince Charles Hospital between 1962 and 1984 are included. Hospital records, electrocardiograms, chest x ray films, haemodynamic data from catheter studies, angiograms, and echocardiograms were reviewed.

Results

There were 35 cases of which 18 were female and 17 male. Simple Ebstein's anomaly was present in 27 patients and eight had other complicating cardiac lesions, most of which affected the right ventricular outflow tract. Additional pulmonary valve stenosis

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Accepted for publication 22 July 1985

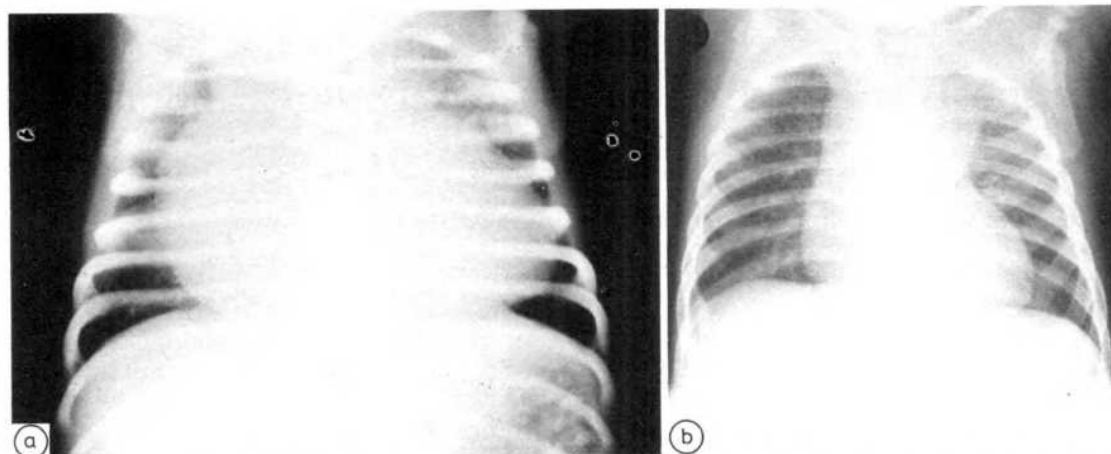


Fig. 1 Chest x ray films of a baby with Ebstein's anomaly showing (a) massive cardiomegaly and oligoemic lung fields at 1 day and (b) aged 5 months, showing that the size of the heart is considerably reduced and that the lung fields are normal.

was present in three, pulmonary atresia in two, a double outlet right ventricle with pulmonary stenosis in one, and two had corrected transposition of the great arteries with coarctation of the aorta.

PRESENTATION

Fourteen patients presented as neonates, 13 of them had cyanosis and a murmur and one had gross hydrops fetalis and supraventricular tachycardia (rate > 300 beats per minute). Ten patients presented as infants and children, five with a murmur, three with supraventricular tachycardia, one with cyanosis, and one with widespread oedema.

Eleven patients did not present until they were adolescents or adults; three of them were over fifty. Palpitation, dyspnoea, and chest pain were the presenting features in seven, while two were found to have cardiomegaly on chest x ray film and two younger patients aged 16 and 25 had asymptomatic murmurs.

Neonates

Of 14 neonates, 12 presented on the first day of life and all had both cyanosis and a murmur. Eleven had loud pansystolic murmurs at the left sternal edge indicative of tricuspid incompetence, and eight of these had an associated thrill, which is a rare finding in a neonate. The cyanosis and murmurs tended to decrease or disappear over subsequent days as the pulmonary vascular resistance fell. The electrocardiograms were not always diagnostic, although 11 of the 14 neonates had right atrial hypertrophy (P wave greater than 3 mm). The QRS axis varied from 30° to 240° . Five had right bundle branch block (QRS duration ≥ 0.06 s), and three had first degree

heart block (PR interval duration ≥ 0.10 s). The cardiothoracic ratio on chest x ray film ranged from 0.51 to 0.90 with a mean of 0.73. The heart size as determined by x ray film became smaller with age (Fig. 1a and b).

The mother of one neonate had taken lithium carbonate in pregnancy. Another had had rubella infection and, in addition to Ebstein's anomaly, her



Fig. 2 Chest x ray film of a 6 year old boy with Ebstein's anomaly showing the classic large rounded "clockface" heart.



Fig. 3 Chest x ray film of a 16 year old boy with Ebstein's anomaly. There is minor right atrial enlargement only.

infant had pulmonary stenosis, cataracts, and deafness.

Children and adults

The cardiothoracic ratio in patients who presented in infancy and childhood ranged from 0.4 to 0.7 (mean 0.57). In adults, it ranged from 0.46 to 0.67 (mean 0.55) (Figs. 2 and 3).

Most patients had either complete or incomplete right bundle branch block evident on the electrocardiogram. Two had evidence of accessory conducting pathways, three are now in atrial fibrillation, and one had complete heart block treated by pacemaker implantation.

Clinical findings in this group were variable and ranged from absent murmur with third or fourth heart sound, through soft mid-diastolic murmurs, to systolic murmurs of from grade 1 to grade 4 or 6 intensity. The anomaly was diagnosed on clinical evidence alone in only one adult.

CARDIAC CATHETERISATION

Catheter studies were done in 25 patients. There was important arrhythmia during the study in 12 patients and two required cardioversion. No deaths

occurred as a result of catheterisation. In 11 infants and children the main pulmonary artery could not be entered; even floatation balloon catheters were not helpful. Three of these patients had associated pulmonary stenosis but the others had a patent right ventricular outflow tract. One such patient was wrongly considered to have pulmonary atresia. There was a right to left atrial shunt in 14. The initial catheter diagnosis was wrong in four patients and was later corrected by restudy in one and by echocardiography in three.

ECHOCARDIOGRAPHY

Echocardiograms were recorded in 29 patients and in 10 they were the only diagnostic investigation. Earlier M mode studies to determine the delay of tricuspid valve closure on mitral closure were not always diagnostic. The delay ranged from 20 to 90 ms and should be ≥ 50 ms for diagnosis of Ebstein's anomaly.^{7,8} Cross sectional studies from the apical four chamber view were most helpful, particularly for measurement of septal leaflet displacement which is always ≥ 15 mm in patients with Ebstein's anomaly (Fig. 4). In the past three years 14 new cases of Ebstein's anomaly have been diagnosed by echocardiography. Other features noted on echocardiography were tethering of the septal leaflet of the tricuspid valve, exaggerated sail-like motion of the anterior leaflet, and the sizes of the atrialised portion of the right ventricle and of the functional right ventricle.

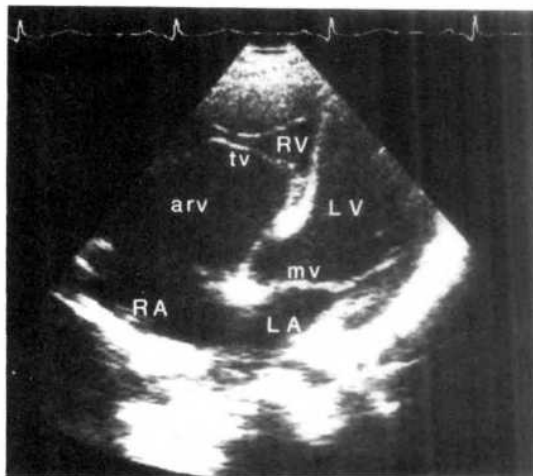


Fig. 4 Cross sectional echocardiogram in the four chamber apical view of a 7 year old boy with Ebstein's anomaly. The tricuspid valve (tv) is displaced 25 mm into the body of the right ventricle (RV) as compared with the mitral valve (mv). This produces a small functional RV and an atrialised portion of right ventricle (arv). The left atrium (LA) and left ventricle (LV) are normal.

FOLLOW UP

Six (17%) of the 35 patients have died. Four deaths occurred in patients with associated abnormalities. Two died of supraventricular tachycardia—a 2 week old boy with a double outlet right ventricle and a girl aged 3 months with pulmonary atresia. Two patients died of infections—one aged 3 months with pulmonary atresia and viral pneumonia and one aged 2 years with pulmonary stenosis, a hypoplastic right ventricle, and pneumococcal septicaemia. One neonate who was wrongly thought to have associated pulmonary atresia died and there was one post-operative death after attempted tricuspid valve replacement and atrial septal defect closure in a 3 year old child.

Only two of our patients have had definitive surgery and one of them died (see above). The other had a closure of an atrial septal defect, pulmonary valvotomy, and tricuspid valve repair and a later tricuspid replacement. Operation in another six patients included one pulmonary valvotomy, one aortopulmonary shunt, two coarctation repairs, one division of a Kent bundle for Wolff-Parkinson-White syndrome, and one pacemaker insertion for complete heart block.

Thirteen patients are currently symptom free, including seven who presented with cyanosis as neonates. Another 12 patients have had slight symptoms such as palpitation or mild dyspnoea. Four have had more serious problems including two with arrhythmias and systemic embolism, one with severe arrhythmias necessitating Kent bundle division, and one who is currently cyanosed and has limited exercise tolerance.

Six women with Ebstein's anomaly have been pregnant; they have a total of 12 children. No deterioration in cardiac function was noted as a result of pregnancy. Eight of the pregnancies occurred before the diagnosis of the cardiac lesion had been established.

Discussion

Neonates presenting on the first day of life with Ebstein's anomaly form an interesting subgroup in which clinical improvement occurs with age. The initial striking presentation is related to persistent pulmonary hypertension with consequent poor forward blood flow through the pulmonary valve, pronounced tricuspid regurgitation, and right to left shunting through the foramen ovale. These result in appreciable cyanosis and loud tricuspid regurgitant murmurs associated with a thrill. As pulmonary vascular resistance falls, forward blood flow improves, and cyanosis and murmur intensity decline as regurgitation becomes less. We have endeavoured to assist

the fall of pulmonary artery pressure by the administration of oxygen to such infants.

These haemodynamic abnormalities explain the difficulties encountered during cardiac catheterisation. The main pulmonary artery could not be entered in 11 of our young patients, eight of whom had a patent right ventricular outflow tract, while three had pulmonary stenosis. Difficulty in entering the pulmonary artery and the right ventricle has been noted previously,⁹ as has the problem of distinguishing between functional and structural pulmonary atresia.¹⁰ One of our patients who died was wrongly considered to have associated pulmonary atresia. Retrograde aortography and contrast and Doppler echocardiography have shown pulmonary regurgitation across structurally normal pulmonary valves in such infants.^{10,11} As the clinical condition of these babies improved there was an associated improvement in the radiological appearance of the heart and lungs. Cardiomegaly due to massive right atrial dilatation lessened and reduced pulmonary vascularity became normal.

Arrhythmias are known to occur during cardiac catheterisation and may result in death. In an international cooperative study of 505 cases of Ebstein's anomaly, 363 catheterisations were done, 90 cases had atrial arrhythmias and there were 13 deaths and six cardiac arrests.¹² Wood stated that when the clinical diagnosis of Ebstein's anomaly is well founded, catheter study is contraindicated because of the risk of death from arrhythmia.¹³ Because cross sectional echocardiography now provides a reliable assessment of anatomy and function, invasive investigation of these patients is no longer necessary.

Echocardiography also led to the correct diagnosis in patients in whom the clinical features were not pathognomonic, and we have used this technique to diagnose 14 new cases in the past three years. In addition four wrong diagnoses based on catheter studies were corrected. The apical four chamber view is the best for cross sectional echocardiographic diagnosis. This allows the atrioventricular ring to be imaged simultaneously with the displaced tricuspid valve leaflets and demonstrates the size of the atrialised portion of the right ventricle.¹⁴ Since the tricuspid valve is normally slightly displaced apically in comparison with the mitral valve, diagnostic criteria are necessary to distinguish the displacement caused by Ebstein's anomaly. From anatomical and echocardiographic studies, a displacement of 15 mm in children and 20 mm in adults has been found to be discriminatory.¹⁵ Another study related the displacement distance of the septal leaflet of the tricuspid valve to the body surface area and showed that a displacement index of $\geq 8 \text{ mm/m}^2$ was a sensi-

tive indicator of Ebstein's anomaly.¹⁶ Apart from its usefulness in primary diagnosis, cross sectional echocardiography was valuable in assessing patients for operation and deciding preoperatively which patients required plastic repair for plication of the atrialised right ventricle and tricuspid annuloplasty rather than tricuspid valve replacement.¹⁷

Possible prognostic factors in Ebstein's anomaly have been assessed in several studies and those features associated with poor outcome were: (a) other complicating cardiac lesions; (b) persistent cyanosis as a result of right to left atrial shunting; (c) diagnosis made in infancy; (d) severe cardiomegaly; (e) development of dyspnoea at rest; and (f) right heart failure.^{8,9,18,19}

Our experience confirms that the outcome is poor in patients with associated cardiac lesions. Four of six deaths in our series were in this category. We do not, however, agree that diagnosis in infancy is a prognostic factor in itself. The condition of neonates usually improved when they had simple Ebstein's anomaly and seven are currently symptom free. Although five of 14 patients presenting as neonates have subsequently died, only one had an uncomplicated lesion. In one case an incorrect diagnosis of pulmonary atresia was made, and because a duct dependent situation was assumed, oxygen treatment was not given. Thus no assistance was given to reduce pulmonary hypertension.

Since operation for Ebstein's anomaly has been associated with a high mortality rate,¹² operation has not been recommended unless patients have severe symptoms. Recent surgical results are better²⁰ but there is still no indication to recommend early surgery when it is evident that many patients with this anomaly remain symptom free or have only mild symptoms for years.

An association between the use of lithium carbonate during pregnancy and Ebstein's anomaly has been reported.²¹ The mother of one of our infants had taken lithium. An association between maternal rubella and Ebstein's malformation has also been reported.²²

Our series of six women with Ebstein's anomaly who had 12 pregnancies is large in comparison with the case reports^{23,24} and small series²⁵ previously reported. Our experience confirms previous conclusions that women who are not cyanosed and have mild Ebstein's anomaly may successfully and safely complete a normal pregnancy.

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Spectrum of congenital heart disease detected echocardiographically in prenatal life

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SUMMARY The spectrum of congenital heart disease seen in a series of 72 fetal anomalies detected echocardiographically differed from that seen in infancy. This reflects the selection of patients for referral for fetal echocardiography and the high rate of natural fetal loss that occurs when severe cardiac defects are present.

It was our impression, based on five years' experience of fetal echocardiography for the prenatal detection of congenital heart disease, that a higher proportion of the cases diagnosed in utero have had severe malformations than do cases presenting in infancy.^{1,2} Cardiac abnormalities seen at abortion and stillbirth are more severe than those diagnosed after birth.³⁻⁵ We have reviewed the spectrum of cardiac anomalies encountered in 72 fetuses with malformed hearts that were identified by echocardiography.

Patients and methods

Patients were referred for fetal echocardiography for the following reasons: a family history of congenital heart disease; exposure to a teratogen (such as lithium, phenytoin, or rubella) in early pregnancy; the detection of non-immune hydrops fetalis; fetal arrhythmia; or an extracardiac anomaly such as exomphalos, neural tube defects, or renal abnormalities. Others were referred because a possible cardiac anomaly was reported at obstetric ultrasonography—usually because of an increase in the size of the heart or a failure to identify four cardiac chambers.

Congenital heart diseases were classified in order of importance (Table 1). The dominant lesion in

each heart was selected by a modification of the methods proposed by Fyler *et al.*¹ and Scott *et al.*² The nomenclature used is that of Tynan *et al.*⁶ Hearts with more than one lesion were classified according to the more important lesion. Thus coarctation coexisting with a ventricular septal defect was classified as *coarctation*. In contrast,

Table 1 Classification of congenital heart disease by the dominant lesion in complex cases. (Diagnoses are listed in decreasing order of importance.)

Absent atrioventricular connection
Double inlet atrioventricular connection
Atrioventricular discordance with ventriculoarterial discordance (congenitally corrected transposition)
Hypoplastic left heart syndrome
Truncus arteriosus
Atrioventricular concordance with ventriculoarterial discordance (complete transposition)
Interrupted aortic arch
Atrioventricular septal defect
Double outlet ventricle
Coarctation of aorta
Absent pulmonary valve syndrome
Ebstein's anomaly
Pulmonary atresia
Tetralogy of Fallot
Pulmonary stenosis
Cor triatriatum
Total anomalous pulmonary venous connection
Aortopulmonary window
Hypertrophic obstructive cardiomyopathy
Aortic stenosis
Persistent ductus arteriosus
Pulmonary artery anomalies
Atrioventricular valve anomalies
Myocardial disease
Atrial isomerism
Peripheral pulmonary stenosis
Systemic arteriovenous fistula
Pulmonary arteriovenous fistula
Secundum atrial septal defect

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coarctation and absence of the left atrioventricular connection, that is right atrium connected to a dominant left ventricle and with a discordant ventriculoarterial connection was classified as *absent left connection*. Atrioventricular septal defect when it coexisted with double outlet right ventricle or pulmonary atresia was classified as atrioventricular septal defect. Conversely, in cases where a common atrioventricular valve was committed predominantly to one ventricle (the other ventricle being rudimentary and hypoplastic) the constellation was coded as *double inlet ventricle*. We considered Ebstein's anomaly to the more important lesion when it coexisted with pulmonary stenosis or atresia and have therefore placed it higher in the list than it appears in the series of Scott *et al*² and Fyler *et al*.¹ Only one diagnosis was recorded for each case. The classification will underestimate the total frequency of conditions such as pulmonary stenosis, coarctation, or ventricular septal defect because they appear at the bottom of the list, even though they are common components of complex disease. This must be taken into account when our data are compared with others in which this classification was not used.

In preparing our table of results (Table 2) we

made some changes to the previous studies of heart disease in infancy.^{1,2} We did not include persistent patency of the arterial duct (ductus arteriosus) because this is a normal readily identifiable fetal structure. Atrial isomerism, which was present in nine of our cases, was not a primary diagnosis in any, and has also been omitted from the list. Absent left connection with double outlet right ventricle has been added to the list. We defined hypoplastic left heart syndrome as the combination of obstruction at the mitral and aortic valves. Isolated mitral atresia was designated as absent left connection and isolated aortic atresia as aortic atresia. Ebstein's anomaly, interrupted aortic arch, and cardiac tumours have been added to the list.

In the first part of our analysis we compared prenatal diagnoses with those recognised in infancy by Fyler *et al*¹ and Scott *et al*.² In the second part we compared the diagnoses in our series with a series of cases identified at abortion³ and in two stillbirth series.^{4,5} The abortion series was compared directly with our series because the abnormalities recognised could be coded in the same way. This was not possible for the stillbirth series. We therefore listed these cases according to the assigned diagnoses.

Results

A cardiac malformation was identified by fetal echocardiography in 72 fetuses. Sixty seven of these fetuses died. In all the malformation was confirmed at necropsy. There were 34 terminations of pregnancy, 13 intrauterine deaths, and 20 neonatal deaths. There are five survivors, three have not yet been delivered and in two the diagnosis was confirmed by postnatal echocardiography and catheterisation and at operation. Of these two, one had complete transposition (the combination of concordant atrioventricular and discordant ventriculoarterial connections) and one had aortic coarctation.

The diagnoses in the whole group were compared with the diagnoses of those presenting in the first year of life (Table 2). There are some obvious differences between the series. In our 72 cases there was a relative paucity of ventricular septal defects, pulmonary stenosis, atrial septal defect, and total anomalous pulmonary venous connection. There was also an excess of absent left atrioventricular connection, interrupted aortic arch, pulmonary atresia with intact septum, atrioventricular septal defect, myocardial disease, Ebstein's anomaly, and cardiac tumour in our series.

Table 3 compares our series with a large stillbirth series⁴ and a more recent stillbirth study.⁵ There were more atrial and ventricular septal defects in the

Table 2 Percentage distribution of heart disease in three series

Diagnosis	Guy's series (n = 72)	Brompton series (n = 1653)	NERICP series (n = 2381)
Ventricular septal defect	9.7	15.4	15.7
Complete transposition	5.5	10.4	9.9
Tetralogy of Fallot	8.3	9.9	8.9
Interrupted arch	4.1	—	—
Coarctation	6.8	10.5	7.5
Hypoplastic left heart	5.5	3.7	7.4
Absent left atrioventricular connection	5.5	—	—
Critical aortic stenosis or aortic atresia	2.7	1.1	1.9
Atrioventricular septal defect	13.8	3.9	5.0
Pulmonary stenosis	—	3.0	3.3
Pulmonary atresia	6.8	1.9	3.1
Atrial septal defect	—	0.5	2.9
Total anomalous pulmonary venous connection	—	3.6	2.6
Myocardial disease	11.1	2.7	2.6
Tricuspid atresia	2.7	4.7	2.6
Double inlet	2.7	4.3	2.4
Double outlet right ventricle	1.3	3.0	1.5
Truncus arteriosus	1.3	2.1	1.4
Ebstein's anomaly	5.5	—	—
Tumour	4.1	—	—
Corrected transposition of great arteries	1.3	0.8	0.9
Others	1.3	11.3	10.4
Patent ductus arteriosus*	—	6.7	10.1
Atrial isomerism*	—	—	—

NERICP, New England Regional Infant Cardiac Program.

*Excluded from Guy's series.

Table 3 Comparison of frequency of congenital heart disease in fetal series and two stillbirth series

Diagnosis	Guy's series (n = 72) (%)	Combined stillbirth series (n = 265) ⁴ (%)	Stillbirth series (n = 81) ⁵ (%)
Ventricular septal defect	9.7	34.7	32.1
Complete transposition	5.5	9.1	3.7
Tetralogy of Fallot	8.3	8.4	8.6
Interrupted arch	4.1	—	—
Coarctation	6.8	9.4	3.7
Hypoplastic left heart	5.5	3.0	7.4
Absent left connection	5.5	—	—
Double inlet	2.7	6.4	2.5
Tricuspid atresia	2.7	—	1.2
Critical aortic stenosis	2.7	0.0	1.2
Atrioventricular septal defect	13.8	6.8	6.2
Pulmonary atresia, intact ventricular septum	6.8	1.1	7.4
Atrial septal defect	—	10.2	3.7
Tumour	4.1	—	—
Double outlet right ventricle	1.3	0.4	7.4
Pulmonary stenosis	—	1.1	—
Myocardial disease	11.1	0.0	—
Truncus arteriosus	1.3	6.0	3.7
Ebstein's anomaly	5.6	—	—
Miscellaneous	1.3	6.4	11.2

two stillbirth series and an excess of cases of interrupted aortic arch, absent left or right atrioventricular connection, atrioventricular septal defect, myocardial disease, Ebstein's anomaly, and cardiac tumours in our series.

Table 4 compares our series and a study of cases obtained from spontaneous abortions. There are fewer cases of tetralogy of Fallot, tricuspid atresia,

Table 4 Comparison of frequency of congenital heart disease in fetal series and abortion series

Diagnosis	Guy's series (n = 72) (%)	Abortion material (n = 38) (%)
Ventricular septal defect	9.7	10.4
Complete transposition	5.5	2.7
Tetralogy of Fallot	8.3	15.6
Interrupted arch	4.1	5.3
Coarctation	6.8	5.3
Hypoplastic left heart	5.5	2.7
Absent left atrioventricular connection	5.5	7.9
Critical aortic stenosis	2.7	2.7
Atrioventricular septal defect	13.8	10.4
Pulmonary atresia, intact ventricular septum	6.8	—
Total anomalous pulmonary venous connection	—	2.7
Myocardial disease	11.1	—
Tricuspid atresia	2.7	7.9
Double inlet	2.7	—
Double outlet right ventricle	1.3	10.4
Truncus arteriosus	1.3	2.7
Ebstein's anomaly	5.5	—
Tumour	4.1	—
Corrected transposition of great arteries	1.3	5.3
Others	1.3	7.9

and double outlet right ventricle in our series. Pulmonary atresia with intact ventricular septum, myocardial disease, Ebstein's anomaly, and cardiac tumours were more common in our series. There was a notable similarity between the frequency of all septal defects and of left sided lesions in the two groups.

Discussion

Many of the differences between the series can be accounted for by the selection of patients for referral for fetal echocardiography. Few mothers who have had children with mild heart disease (for example, septal defects or pulmonary stenosis) are referred for examination. Whereas mothers who have had a child who died of major congenital heart disease are more likely to be referred.

Some defects are over-represented in our series as compared with all the other series. These are pulmonary atresia with intact septum, myocardial disease, Ebstein's anomaly, and cardiac tumours. In the fetus pulmonary atresia with intact septum and Ebstein's anomaly both produce gross cardiac enlargement that is readily recognisable at routine ultrasonography. It is perhaps surprising that these defects were less commonly recognised in the series of stillbirths and aborted fetuses, since of our nine cases with these two diagnoses, one resulted in spontaneous abortion and five in stillbirths. The high frequency of myocardial disease seen in our series is due to the selection of pregnancies where renal anomalies have been detected in the fetus. These cases have hypertrophic cardiomyopathy with echocardiographic evidence of obstruction to left ventricular outflow, such as midsystolic closure of the aortic valve and systolic anterior motion of the mitral valve. Hypertrophic cardiomyopathy has been reported in association with renal disease.⁷ Fetal cardiac tumours present with evidence of obstruction to cardiac output and intrauterine cardiac failure and two of our three cases died in utero. In one the pregnancy was terminated. This high incidence of fetal loss secondary to cardiac tumour may account for the rarity of this lesion after birth.

Atrioventricular septal defect was more common in our series than it was after delivery. This also can partly be accounted for by the high rate of fetal loss. Of 12 cases with this diagnosis only two were associated with chromosome anomalies. Six pregnancies were terminated, two cases died after birth, but four cases died in utero. This high rate of fetal loss was also found in the spontaneous abortion series, in which the frequency of atrioventricular septal defects resembled our results.³

The greatest disparity in all the comparisons is

between the present series and the stillbirth series. This may be accounted for by differences in coding diagnosis or inaccuracy of diagnosis in the stillbirth series. If some of the ventricular septal defects reported in the stillbirth series were cases of tetralogy of Fallot or atrioventricular septal defect, the studies might become more similar. Because the abortion series and the two stillbirth series were reported by specialists in congenital heart disease, criteria for diagnosis and nomenclature are more likely to be consistent. Furthermore, they used the same coding system and thus differences between the series are likely to be real. The difficulties in comparing different series, however, emphasise the importance of an international, common nomenclature and method of classification of diagnosis in congenital heart disease.

In summary, there are major differences between the spectrum of congenital heart disease seen prenatally and postnatally. Complex defects are more common prenatally. This is partly accounted for by the selection of patients for referral for fetal echocardiography but also perhaps by the unexpectedly high rate of fetal wastage when such defects are severe. An accurate picture of the true prevalence of congenital heart disease requires a large prospective study of an unselected series of pregnancies. Cases will be missed unless all fetuses are studied by echocardiography and are followed up postnatally by paediatric cardiologists; when abortion occurs the fetus must be expertly examined. The current simplicity and accuracy of fetal echocardiography⁸

makes this by no means an impossible proposition.

Dr Allan, Dr Crawford, and Professor Anderson are supported by the British Heart Foundation, the latter in association with the Joseph Levy Foundation.

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Descending aortography with balloon inflation

A technique for evaluating the size of persistent ductus arteriosus in infants with large proximal left to right shunts

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SUMMARY Six infants underwent angiography of the aortic root and the descending aorta with balloon inflation during diagnostic cardiac catheterisation and angiography. In these infants with large proximal left to right shunts, descending aortography with balloon inflation resulted in better opacification of the persistent ductus arteriosus than aortic root angiography, thereby enabling accurate measurement of the persistent ductus arteriosus. Similar systemic and pulmonary vascular impedances had been speculated as the cause of poor or non-opacification of the ductus after ascending aortography. Balloon inflation may have altered the aortic impedance with resulting opacification of the ductus. Descending aortic angiography with balloon inflation is also useful in opacifying the isolated ductus and in demonstrating aortopulmonary collaterals in patients with pulmonary atresia.

Persistent ductus arteriosus in patients with large ventricular septal defects predisposes to pulmonary vascular obstructive disease unless early intervention is carried out.^{1,2} Selective aortic root angiography has, therefore, been recommended in all patients with large ventricular septal defect to diagnose the presence of persistent ductus arteriosus.^{2,3} Rao *et al*⁴ and others³ have previously shown that selective aortography does not uniformly detect the ductus in the presence of a large proximal shunt (ventricular septal defect or atrioventricular canal). We suggested that in this group of patients a persistent ductus might be diagnosed best by passing a catheter across the ductus arteriosus and specifically probing for it.⁴ Although diagnosis can be made by passage of the catheter across the ductus, the size of the ductus cannot be assessed. The purpose of this study was to assess the ability of descending aortography with balloon inflation to determine the exact size of the persistent ductus arteriosus.

Patients and methods

Six infants aged 2 to 8 months underwent diagnostic catheterisation and angiography for evaluating large ventricular septal defect and suspected additional ductus arteriosus. All but one had normally related great arteries; one had transposition of the great arteries. A common atrioventricular canal was present in one infant. A No 5 French gauge catheter with multiple side holes was advanced from the right ventricle into the ascending aorta via the ventricular defect. In the infant with transposition the catheter was advanced directly from the right ventricle into the ascending aorta. Renografin (76%), 1 ml/kg body weight, was injected over 1.5 s into the aortic root, while cineangiograms were recorded in the posteroanterior and lateral projections. The catheter was then replaced with a No 5 French gauge balloon angiographic catheter (with injection holes proximal to the balloon) and was advanced from the main pulmonary artery into the descending aorta via the ductus. In the patient with transposition, the catheter was advanced from the ascending aorta into the descending aorta. The catheter tip was positioned in the mid-thoracic aorta, and the balloon was inflated with carbon dioxide during the initial phases of cine-

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Accepted for publication 1 July 1985

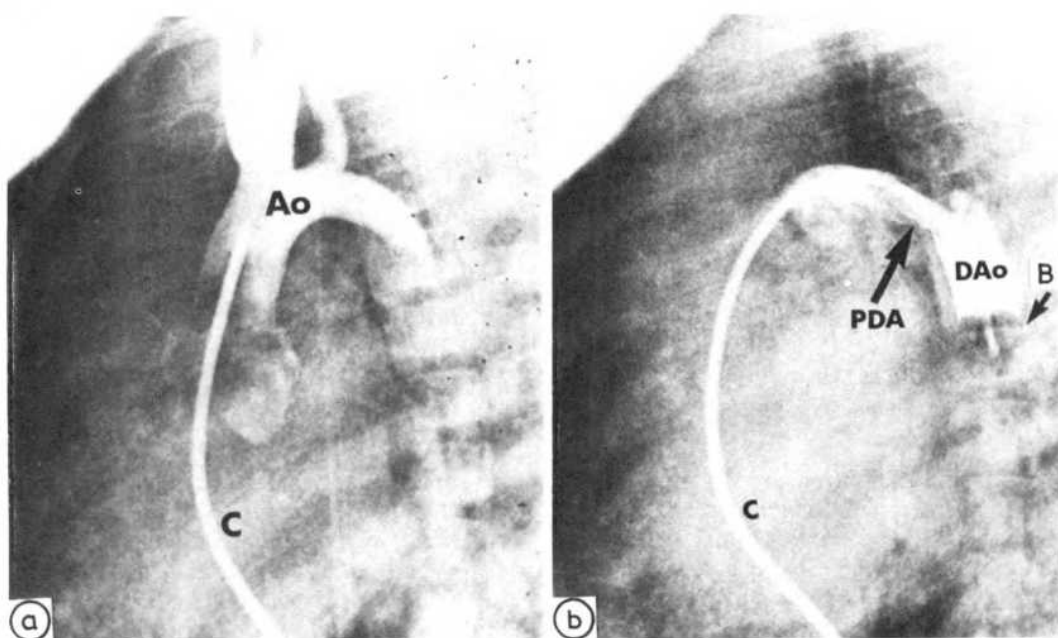


Fig. 1 A selected cineangiographic frame from an aortogram in the lateral view (a). The catheter (C) has been advanced into the aorta (Ao) from the right ventricle via ventricular septal defect. There was no visualisation of a ductus arteriosus on careful review of the cineangiogram. A cineangiographic frame that best opacifies the entire aorta was chosen for illustration. The same infant's descending aortogram (b) with the balloon (B) inflated shows the persistent ductus arteriosus (PDA) clearly. The catheter had been advanced into the descending aorta (DAo) from the main pulmonary artery through a PDA.

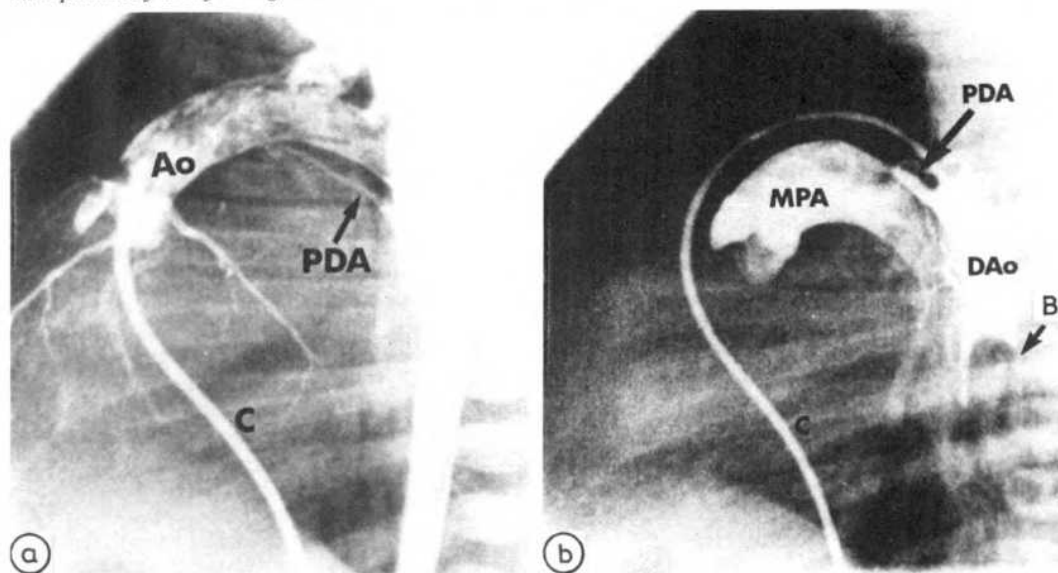


Fig. 2 A cineangiographic frame from the lateral view of an aortogram (a) of an infant with transposition of the great arteries and a large ventricular septal defect. The catheter (C) had been advanced into the ascending aorta (Ao) directly from the right ventricle. Note the threadlike, small persistent ductus arteriosus (PDA). In the same infant the catheter had been advanced into the descending aorta (DAo) and the balloon (B) was inflated during the initial phases of the angiography (b). Note the clear cut delineation of the PDA and pronounced opacification of the main pulmonary artery (MPA).

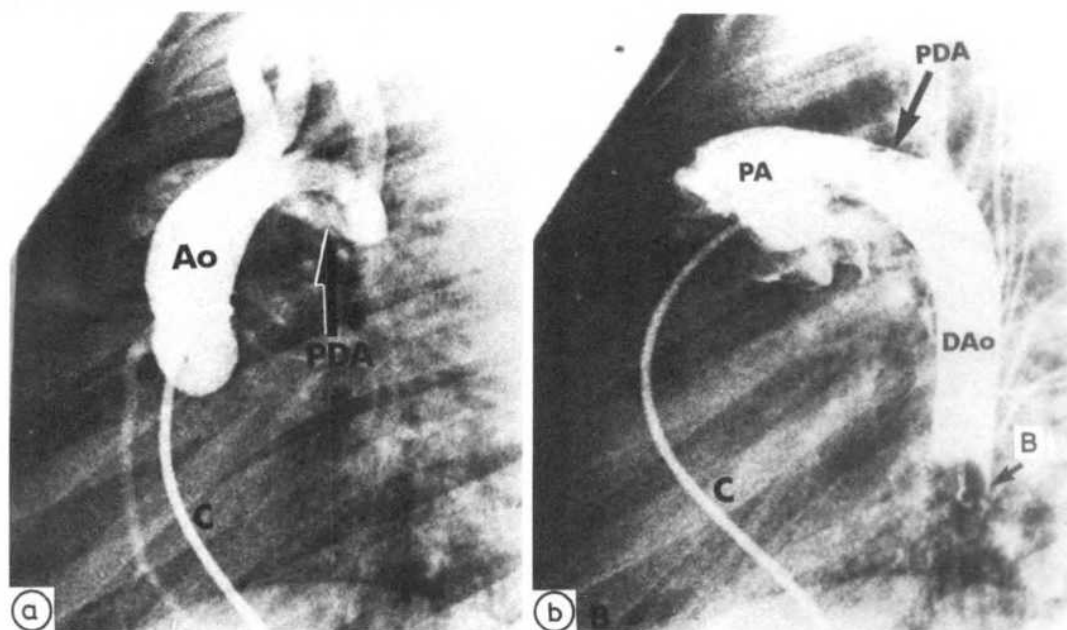


Fig. 3 Aortogram (a) showing opacification of persistent ductus arteriosus (PDA). When a descending aortogram (b) was performed with the balloon (B) inflated, a large PDA with opacification of pulmonary arteries (PA) was seen. Note the discrepancy in the size of PDA between both aortograms. The course of the catheter (C) was similar to that described in Fig. 1.

angiography while exactly the same amount of contrast material was used as in the aortic root angiography; the total calculated contrast material was injected over 1.5 s. Descending aortography was also recorded in the posteroanterior and lateral projections. No complications were encountered during the procedure.

To evaluate any adverse effects of balloon inflation in the descending aorta, aortic pressure (proximal to the balloon) and an electrocardiogram were recorded before and during balloon inflation in five other infants.

Results

During aortic root angiography faint or partial opacification of the persistent ductus occurred in four infants and no opacification in the remaining two. During descending aortic angiography the ductus arteriosus was opacified in all infants, was seen more clearly, and was much larger in each case (Figs. 1–3). The ductus was either not visualised or only partially visualised in the ascending aortic angiogram; in the descending aortic angiogram with the balloon inflated the size of the ductus could be clearly determined.

The mean (SD) systolic pressure (90 (8) mm Hg) in the descending aorta proximal to the inflated bal-

loon increased (110 (5) mm Hg) significantly ($p < 0.01$) during balloon inflation, whereas the diastolic and mean blood pressures did not change significantly ($p > 0.1$). A decrease in mean (SD) heart rate (114 (7) to 96 (17) beats/min) was noted, but this difference did not attain statistical significance. In addition, no clinically detectable adverse side effects were noted either in these infants in whom both the aortic pressure and electrocardiogram were recorded during balloon inflation or in the infants in whom descending aortography with balloon inflation was performed.

Discussion

The possible explanations for non-opacification of a ductus arteriosus during aortic root angiography in patients with large proximal left to right shunts have been discussed elsewhere.^{3,4} We looked at the known physiological determinants of left to right shunting—namely, pulmonary vascular resistance, the ratio of pulmonary vascular resistance to systemic vascular resistance, and the ratio of pulmonary artery pressure to aortic pressure—and found that these could not account for the non-opacification of a ductus arteriosus.⁴ Many other physiological variables determined at cardiac catheterisation and technical aspects of angiography were scrutinised, but

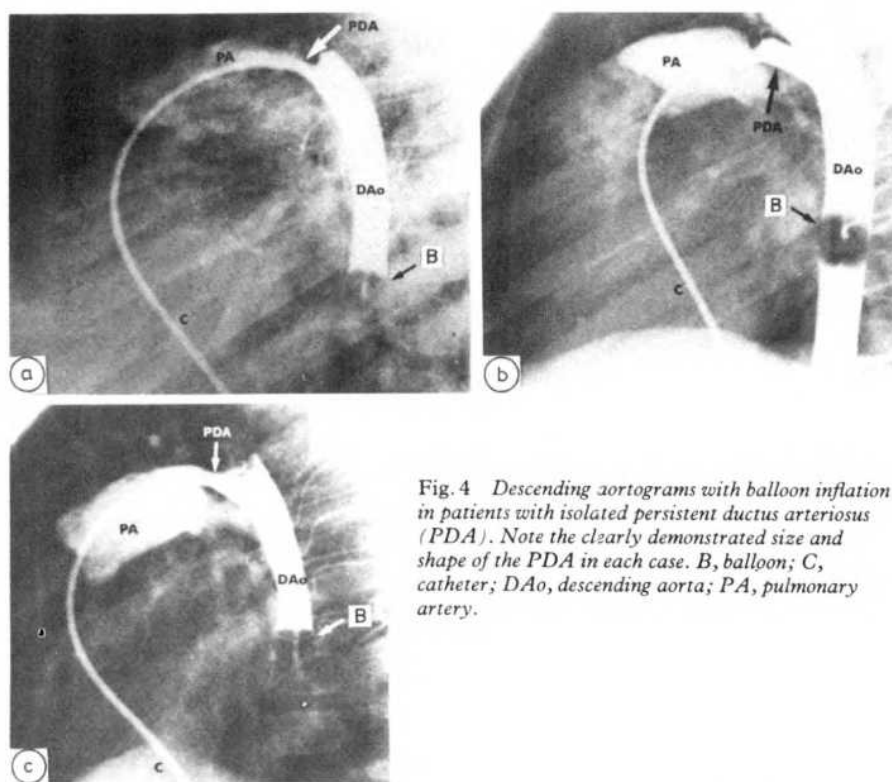


Fig. 4 Descending aortograms with balloon inflation in patients with isolated persistent ductus arteriosus (PDA). Note the clearly demonstrated size and shape of the PDA in each case. B, balloon; C, catheter; DAo, descending aorta; PA, pulmonary artery.

none explained the phenomenon. Poor visualisation of the ductus during aortic root angiography may have been related to the small size of the catheter (No 5 French gauge) and the "small" dose (1 ml/kg) of contrast medium used. With regard to the size of the catheter: firstly, the infants were very young (2–8 months) and their weight was low; but secondly, and more importantly, the calculated contrast material was delivered over 1.5 s. Furthermore, the descending aortography was also performed with a similar sized catheter. The amount of contrast material used (1 ml/kg) was comparable to that recommended for standard aortography (0.75 to 1.0 ml/kg) by several groups of workers in this field.^{5–7} Again, the same quantity of contrast material was used during descending aortography. For these reasons neither the size of the catheter nor the amount of contrast material used was responsible for faint or non-opacification of the ductus during aortic root angiography. We have speculated that the lack of difference in the vascular impedance (the instantaneous pressure to flow relation) between the interconnected circulations (systemic and pulmonary) may help explain the non-opacification of a ductus arteriosus.⁴ In the present study, inflation of the balloon during angiography with a resulting increase in

the systemic pressure may have altered the aortic impedance, producing more complete opacification of the ductus arteriosus.

Other methods of demonstrating ductus arteriosus include aortography at the level of ductus after the catheter has been advanced from the pulmonary artery via the ductus into the aorta, retrograde femoral artery catheterisation,^{8–10} aortography by countercurrent injection via the radial artery,^{11,12} and transductal aortic arch angiography.^{13,14} In my experience, aortography with the catheter positioned at the level of the ductus arteriosus after having crossed it does not produce consistent visualisation of the ductus arteriosus. Despite recent advances in retrograde arterial catheterisation and countercurrent injection in small infants and children,^{15,16} these procedures are sometimes associated with complications and technical difficulties.^{15–23} Transductal aortic arch angiography that Mardini and Rao previously described,^{13,14} although useful, did not produce as good an opacification of the ductus as did descending aortography with balloon inflation. This technique of descending aortography with balloon inflation is safe. When the aortic pressure and heart rate were recorded during balloon inflation there

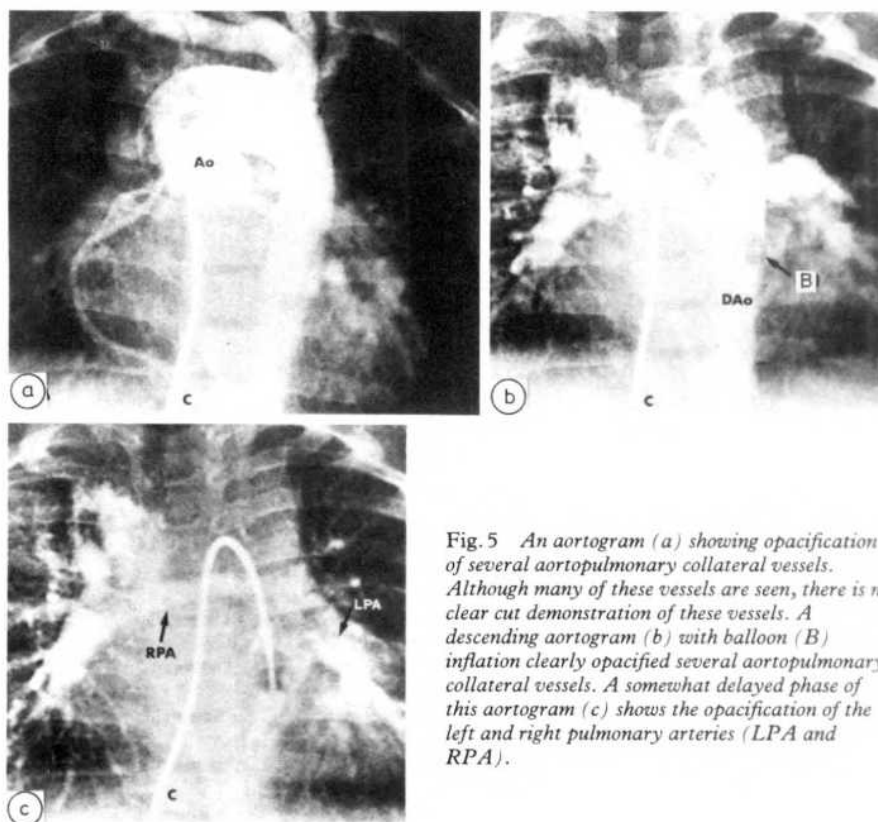


Fig. 5 An aortogram (a) showing opacification of several aortopulmonary collateral vessels. Although many of these vessels are seen, there is no clear cut demonstration of these vessels. A descending aortogram (b) with balloon (B) inflation clearly opacified several aortopulmonary collateral vessels. A somewhat delayed phase of this aortogram (c) shows the opacification of the left and right pulmonary arteries (LPA and RPA).

was only a minimal increase in aortic systolic pressure proximal to the balloon and a slight, if any, decrease in heart rate. The latter is probably vagus mediated. No other complications were encountered. Because of the safety and better visualisation of the ductus arteriosus, this technique is recommended for evaluating the size of the ductus arteriosus in patients with large proximal left to right shunts.

CLINICAL APPLICATIONS

Encouraged by the results of descending aortic angiography with balloon inflation in demonstrating the size of the ductus arteriosus, I have since applied this technique to other lesions. Several patients with a clinical diagnosis of ductus arteriosus but with additional abnormal findings were studied to exclude any other associated cardiac defects. Figure 4 shows several examples of descending aortograms with balloon inflation. The size and shape of the ductus were clearly visualised in these cineangiograms. Such information is of great value during transcatheter closure of a persistent ductus.²⁴⁻²⁸

I recommend descending aortography before transcatheter ductal closure so that an appropriate sized ductal plunging device can be chosen/prepared for ductal closure.

It is important to evaluate the pulmonary arterial anatomy in patients with pulmonary atresia with ventricular septal defect ("pseudotruncus") and type IV truncus.²⁹⁻³³ Figure 5a shows an aortic root angiogram with reasonable opacification of the collateral vessel supply to both lungs; but, as can be seen, the collateral vessels were clearly visualised when descending aortography was performed with balloon inflation (Fig. 5b). Furthermore, delayed opacification of the pulmonary arteries (Fig. 5c) was seen after descending aortography. I recommend descending aortography with balloon inflation for delineating the number, location, and size of the aortopulmonary collateral vessels in patients with pulmonary atresia. This should be performed before selective catheterisation and contrast injection of these aortopulmonary collateral vessels.

In conclusion, descending aortography with balloon inflation during the initial phase of the angio-

graphy is a useful and safe technique for evaluating the size of the persistent ductus arteriosus in patients with large proximal left to right shunts. Other clinical applications of this technique include clear cut opacification and anatomical delineation of the isolated ductus before transcatheter closure of the ductus and demonstration of aortopulmonary collateral vessels in patients with pulmonary atresia.

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Asymmetric septal hypertrophy and hypothyroidism in children

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SUMMARY Any echocardiographic study of two children with hypothyroidism demonstrated the presence of asymmetric septal hypertrophy. One child died aged 11 months, and pronounced thickening of the interventricular septum was confirmed at necropsy. There was also hypertrophy of the left ventricular free wall. Histological examination showed only slight muscle fibre disarray, but there was striking vacuolation and hypertrophy of muscle fibres. In the second case, a child aged five years, the asymmetric septal hypertrophy disappeared after 18 months' treatment with L-thyroxine. Furthermore, other indices of myocardial function also returned to normal. The mechanism producing asymmetric septal hypertrophy in hypothyroidism is unknown. These are the youngest cases in which this association has been reported.

Pericardial effusions and pronounced abnormalities in left ventricular function have been demonstrated in hypothyroid adults by echocardiography.^{1,2} Furthermore, Santos *et al* have described patterns of asymmetric thickening or hypertrophy of the interventricular septum and other features compatible with hypertrophic obstructive cardiomyopathy in adults with long standing hypothyroidism.³ These abnormalities were reversed after treatment with thyroid hormone. In the first reported echocardiographic study of 15 hypothyroid children, Hayford *et al* found no appreciable abnormality in cardiac chamber or myocardial dimensions, systolic time intervals, or indices of myocardial contractility compared with a normal population.⁴ Both Nose *et al* and Farooki *et al*, however, found prolonged systolic time intervals in children with primary hypothyroidism, and these indices became normal with treatment.^{5,6} Finally, in a recent study of 12 babies with congenital hypothyroidism, left ventricular systolic and diastolic dimensions, posterior wall

thickness, and end diastolic and systolic volumes were all lower than normal.⁷

We describe two children with hypothyroidism who had echocardiographic features of asymmetric septal hypertrophy. As far as we are aware they are the youngest patients in whom this abnormality has been reported. Asymmetric septal hypertrophy was confirmed at necropsy in one infant. In the surviving patient the abnormality had disappeared 18 months after the start of thyroid treatment.

Case reports

CASE 1

An 11 month old female infant (weight 5.6 kg, length 60 cm, below 3rd percentile) was admitted to hospital because of constipation, lethargy, and poor feeding. She was the second child of normal unrelated parents and had been delivered vaginally at another hospital after an uneventful pregnancy. She had all the clinical features of severe myxoedema including a large tongue, distended abdomen, and dry scaly skin. She cried poorly, had never smiled, and had never attempted to sit. The heart rate was 88 beats per minute and all the pulses were palpable. On auscultation of the heart, a grade 2/6 high-pitched ejection systolic murmur was heard loudest at the third and fourth left intercostal spaces. The liver edge was

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Accepted for publication 2 May 1985

Table 1 *Thyroid function studies*

	Case 1	Case 2		Normal values
		Before treatment	After 3 months of L-thyroxine	
Triiodothyronine uptake (%)	26	22		30-40
Total thyroxine (nmol/l)	14	19		60-150
T7 index	4	0.33		17-60
Free thyroxine index	1	0.2		5-12
Total triiodothyronine (nmol/l)			1.6	0.8-3.5
Free thyroxine (pmol/l)			22.2	10-25
Thyroid stimulating hormone (μ U/ml)	70.5	44.8	2.9	1.5-8

palpable 4 cm below the right costal margin. The lungs were clinically normal. The haemoglobin concentration was 8.1 g/dl.

Bone age was appreciably less than normal with no epiphyses in the humeral heads or the carpal bones. A chest x ray examination showed a cardiothoracic ratio of 0.6 in a hyperinflated chest. The vascularity of the lungs was normal. The electrocardiogram showed a mean frontal QRS axis of $+90^\circ$ and voltages were generally low. A positive "mosque" sign⁸ was present in the right precordial leads (rounded symmetrical T waves), while the left precordial leads showed inverted T waves. Thyroid function tests (Table 1) confirmed the diagnosis of hypothyroidism.

The M mode echocardiogram showed asymmetric

hypertrophy of the interventricular septum with a ventricular septal left ventricular posterior wall ratio of 2:1, and a septal thickness of 10 mm (Table 2).

Systolic anterior motion of the mitral valve was seen. There was also evidence of a pericardial effusion (Fig. 1). Aortic valve motion was normal.

L-thyroxine (0.025 mg daily) was started on the day after admission. Nasogastric tube feeds were started. She collapsed suddenly 24 hours later and had a cardiorespiratory arrest. Resuscitation was unsuccessful.

Necropsy findings A small fibrosed thyroid gland was present in the usual position. Microscopically this gland consisted mainly of fibrous tissue with a few haphazardly interspersed small follicles. The pericardial sac contained 50 ml of clear straw col-

Table 2 *Echocardiographic measurements (M mode)*

	Case 1	Case 2		
		Before treatment	After 6 months of L-thyroxine	After 18 months of L-thyroxine
Heart rate (beats/min)	130	88	115	100
Interventricular septum (mm)	10 (3-7)	8 (4-8)	6.5 (4-8)	5.5 (4-8)
LVPW (mm)	5 (2.5-6.5)	5 (3.5-7.5)	5 (3.5-7.5)	5 (3.5-7.5)
Septal LVPW	2.0 (<1.3)	1.6 (<1.3)	1.3 (<1.3)	1.1 (<1.3)
LVPEP (ms)	75 (47-79)	111 (60-91)	62 (52-83)	70 (56-87)
LVET (ms)	205 (171-257)	240 (231-318)	228 (191-278)	260 (211-298)
LVPEP/LVET	0.36 (0.29-0.39)	0.46 (0.29-0.39)	0.27 (0.29-0.39)	0.27 (0.29-0.39)
LVSF (%)	59 (24-46)	65 (24-46)	52 (24-46)	35 (24-46)
VCF (circ/s) (mean (SE))	2.8 (1.34 (0.03))	2.7 (1.34 (0.03))	2.26 (1.34 (0.03))	1.35 (1.35 (0.03))
Isovolumic contraction period (mean (SD) (ms))	—	61 (33 (7))	20 (33 (7))	25 (33 (7))

LVPW, left ventricular posterior wall; LVPEP, left ventricular pre-ejection period; LVET, left ventricular ejection time; LVSF, left ventricular shortening fraction; VCF, velocity of circumferential fibre shortening. Numbers in parentheses are normal values from Latson and Gutgesell,⁹ with the exception of VCF and isovolumic contraction period which are from Goldberg *et al*¹⁰ and Meyer¹¹ respectively.

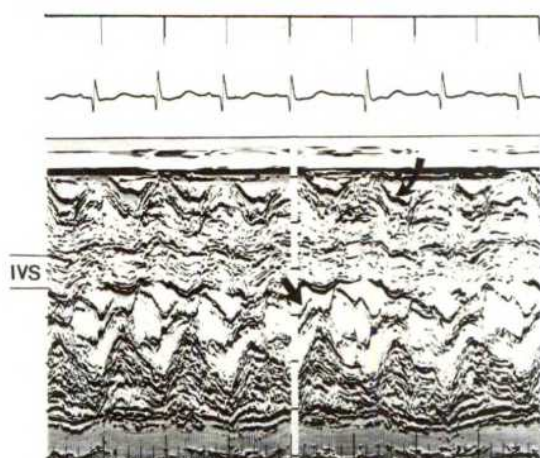


Fig. 1 M mode echocardiogram in case 1 showing pronounced thickening of the interventricular septum (IVS), systolic anterior motion of the mitral valve (straight arrow), and a pericardial effusion (curved arrow).

oured fluid. The heart weighed 66 g (normal (SD) 44 (8) g). This increase in weight was caused by gross asymmetric hypertrophy of the interventricular septum (thickness 10 mm) which merged gradually with thickened left ventricular walls. The septal muscle bulged into the outflow tract of the left ventricle, and the ventricular cavity was small and distorted (Fig. 2). The papillary muscles were large with rounded tips. There was a band of endocardial thickening beneath the aortic valve. The right ventricular wall was only 2 mm thick. Elsewhere in the heart the endocardium was normal. The septum bulged slightly into the right ventricular outflow tract but the free wall of the right ventricle was not affected. The heart valves and coronary arteries were normal.

The microscopic abnormalities were most pronounced in the interventricular septum. The muscle fibres were moderately hypertrophied and there was focal interstitial fibrosis. There were occasional focal areas that showed shortening and abnormal interdigitations of the fibres (Fig. 3a). Thus there was evidence of slight muscle fibre disarray. There was, however, extensive vasculature of the muscle fibres and there were foci of tissue in both anterior and posterior left ventricular walls showing this abnormality (Fig. 3b). The abnormal areas were mingled closely with areas of tissue with normal histological appearance. No inflammatory reaction was present and stains for mucopolysaccharides were negative.

CASE 2

A five year old girl was admitted to hospital because

of short stature. She had a history of constipation. The child was pale and had been investigated for anaemia at 1 year of age. She weighed 13 kg and she was 88.5 cm tall (3rd percentile). Her heart rate was 82 beats per min. She had a sallow and dry skin and looked myxoedematous. There was hypertelorism and a flattened bridge to her nose. The thyroid gland was not palpable. The heart and chest were normal. Her abdomen protruded and she was very constipated. No visceromegaly was noted. Tendon reflexes were all present and equal but there was pronounced slowing of the recovery phase. Chest x ray examination showed a heart of normal size and clear lung fields. The electrocardiogram showed a frontal QRS axis of $+150^\circ$; a positive "mosque" sign, and rather flattened ST-T wave segments. Thyroid function tests confirmed hypothyroidism (see Table 1). The serum cholesterol concentration was 12.03 mmol/l (normal 3.12–6.76 mmol/l) and microsomal antibodies 1:400. Bone age was 18 months on radio-



Fig. 2 Morphological appearance of left ventricle (opened) in case 1 showing pronounced hypertrophy of the interventricular septum and a thickened left ventricular wall. Probe is under the posterior leaflet of the mitral valve. Apex of the left ventricle has been cut in cross section.

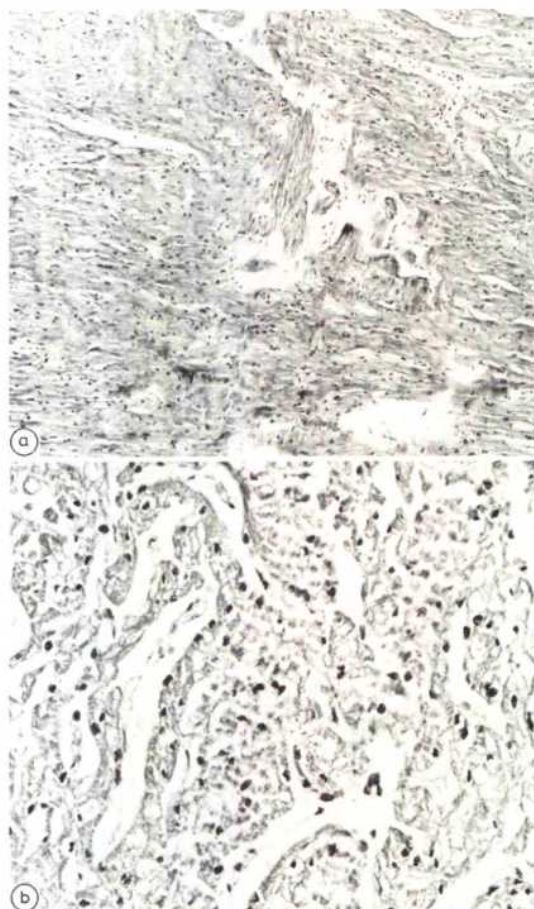


Fig. 3 Photomicrographs in case 1 of (a) interventricular septal myocardium showing abnormal arrangement of muscle fibres (haematoxylin and eosin $\times 132$ (original magnification)). (b) Myocardium from interventricular septum showing extensive intracytoplasmic vacuolation. (Haematoxylin and eosin $\times 532$) (original magnification).

logical assessment. The haemoglobin concentration was 10.4 g/dl.

An M mode echocardiogram (Fig. 4) showed a disproportionately thickened septum with a septum to posterior wall ratio of 1.6:1. The septum was 8 mm thick (normal mean 6 mm; range 4–8 mm). There was pronounced hypercontractility of the left ventricle with a shortening fraction of 0.65 and a velocity of circumferential fibre shortening of 2.7 circ/s. On the other hand, the left ventricular systolic time interval was prolonged—that is the ratio of the pre-ejection period to ejection time was increased.^{9–11} Cross sectional echocardiography confirmed the presence of asymmetric septal hyper-

trophy. There was no systolic anterior motion of the mitral valve, no abnormalities of aortic valve motion, and no pericardial effusion.

Initially a dose of 0.05 mg L-thyroxine was given, and this was later increased to 0.1 mg daily. Thyroid function had become normal three months after the start of treatment (Table 1).

A repeat echocardiogram after six months' treatment showed that the septal to posterior wall ratio had fallen to 1.2:1 (to within normal limits) and the septal thickness was now within one standard deviation of the normal mean. There was still hyperdynamic ventricular contractility, however, with a shortening fraction of 0.52 and a velocity of circumferential fibre shortening of 2.26 circ/s. These values and the left ventricular systolic time intervals became normal 18 months after the start of treatment (Table 2).

Discussion

The two cases we describe suggest that hypothyroidism may be associated with asymmetric septal hypertrophy. Until the recent report by Farooki *et al* we believed them to be the first cases to be described in children.⁶ Their two patients with asymmetric septal hypertrophy and hypothyroidism were much older than ours (8½ and 10 years). Our findings and theirs accord with those of Santos *et al* who reported similar features in adults.³ The fact that Hayford *et al* did not demonstrate cardiomyopathy in children may be related to the duration

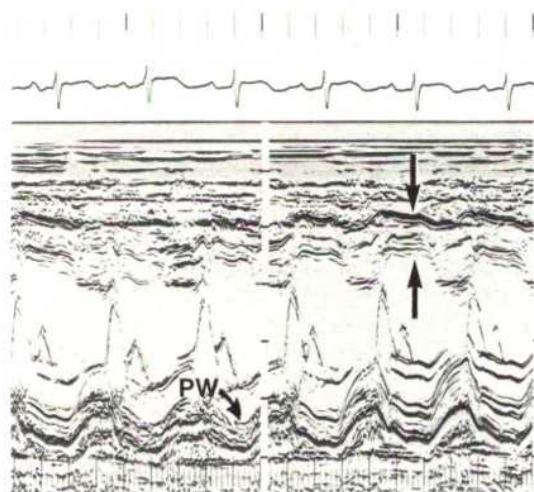


Fig. 4 M mode echocardiogram in case 2 showing thickened interventricular septum (straight arrows) compared with the left ventricular posterior wall (PW). Mitral valve motion is normal.

of the hypothyroidism before cardiac function was studied.⁴ Of their four cases with congenital hypothyroidism, three were less than 6 months of age, while the fourth was 1 year old. Our first case had clearly been hypothyroid from birth (11 months) and in the second case hypothyroidism may also have been present from, or shortly after, birth.

Another interesting echocardiographic finding in our surviving patient was that despite the rapid velocity of circumferential fibre shortening there was a prolonged left ventricular systolic time interval which shortened with thyroxine treatment. This accords with the reports of Nose *et al* and Farooki *et al*, who also noted prolonged left ventricular systolic time intervals in their hypothyroidic children that reversed with treatment.^{5,6}

Pericardial effusion, which was present in the patient who died, is a recognised feature in hypothyroidism in both adults and children.^{14,6} But there were no specific microscopic changes warranting a diagnosis of myxoedematous heart disease.¹² Vacuolation of muscle fibres, which was the most pronounced histological abnormality noted in our patient, has been reported in adults dying of hypothyroidism.¹² The following microscopic abnormalities are generally considered to be those that are most typical of hypertrophic obstructive cardiomyopathy—short runs of fibres interrupted by connective tissue, large bizarre nuclei, fibrosis, degenerating muscle with disappearing myofibrils, and disorganised “whorling” muscle (muscle fibre disarray).^{13,14} None of these abnormalities was readily seen in our first case. Thus it is unlikely that the asymmetric septal hypertrophy in this infant can be attributed to an intrinsic hypertrophic obstructive cardiomyopathy. Nevertheless, the findings of systolic anterior motion of the mitral valve on the echocardiogram and of a band of endocardial thickening beneath the aortic valve at necropsy provide evidence that the patient did indeed have dynamic subaortic stenosis. This might also explain the origin of the high pitched ejection systolic murmur in this child.

Both hyperthyroidism and hypothyroidism may result in asymmetric septal hypertrophy of the interventricular septum. In the early 1970s three cases of hypertrophic cardiomyopathy and hyperthyroidism were described,¹⁵ and it was postulated that hyperthyroidism might act as a stimulus to produce excessive cardiac hypertrophy. Olsen *et al* administered triiodoacetic acid (Triac), a thyroxine analogue, to pregnant rats and induced electronmicroscopic changes typical of hypertrophic cardiomyopathy in the fetal but not in the maternal heart.¹⁶ The mechanism of action of Triac was not known. As result of these studies it was suggested that thyroid function

should be assessed in patients with obscure forms of cardiac disease. Thyroid disease has been detected in 13% of 31 patients with hypertrophic obstructive cardiomyopathy.¹⁷ Recently, *in vitro* experiments with triiodothyronine on isolated fetal mouse hearts in organ culture have been carried out. It was concluded that thyroid hormone directly stimulates cardiac protein synthesis and thus causes cardiac hypertrophy in the absence of major haemodynamic alterations.¹⁸

Paradoxically, Santos *et al* found asymmetric septal hypertrophy (by M mode echocardiography) in 17 of 19 adult patients with untreated hypothyroidism.³ Some of the additional findings were similar to the echocardiographic features of idiopathic hypertrophic subaortic stenosis—for example, systolic anterior motion of the mitral valve. These abnormalities resolved in 10 patients when they became euthyroid on L-thyroxine treatment. The mechanism for the production of these changes is not known.

The findings in our two patients suggest that, as with adults, asymmetric septal hypertrophy can occur in some children with hypothyroidism, and that it may be reversible with treatment. Indeed, this is borne out by the recent report of Farooki *et al* who found asymmetric septal hypertrophy in two of 11 hypothyroid children.⁶ We therefore recommend that echocardiography should be carried out routinely in all babies and children with hypothyroidism, both before and during L-thyroxine replacement treatment.

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Cardiac hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism—an association

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SUMMARY Left ventricular hypertrophy (symmetric, asymmetric, or hypertrophic cardiomyopathy) is an almost invariable accompaniment of primary hyperparathyroidism. Five of 18 patients with hypertrophic cardiomyopathy had raised serum concentrations of parathyroid hormone with normal serum calcium concentrations. Left ventricular hypertrophy did not occur in any of the six patients with hypercalcaemia alone. These relations suggest that parathyroid hormone rather than a rise in the extracellular calcium concentration is associated with a spectrum of left ventricular hypertrophy.

All patients with increased circulating parathyroid hormone concentrations should have echocardiographic examination of the left ventricle. Conversely, parathyroid hormone concentrations should be measured in all patients with left ventricular hypertrophy from an unknown cause, especially those with hypertrophic cardiomyopathy.

Calcium has powerful positive inotropic and chronotropic effects on cardiac muscle.¹ Any factor that promotes transmembrane calcium flux could be involved in the pathogenesis of cardiac hypertrophy.² Prompted by the discovery that left ventricular hypertrophy (symmetric, asymmetric, or hypertrophic cardiomyopathy) is often found in our patients with primary hyperparathyroidism, we have attempted to identify further cases of primary hyperparathyroidism and also to determine whether hormone and calcium concentrations were altered in patients with hypertrophic cardiomyopathy. We also studied patients with hypercalcaemia due to causes other than hyperparathyroidism.

Patients and methods

Forty patients were studied (aged 24-80, mean 63; 15 men, 25 women). Twenty two had been fully investigated because of hypercalcaemia in the metabolic and general medical wards of this hospital at some time during the past two years. (No patient with a blood pressure >150/90 mm Hg was

included.) Sixteen of these patients were found to have primary hyperparathyroidism and six of these had had operations to remove either a parathyroid adenoma or a hyperplastic gland. The remaining six of the 22 patients were hypercalcaemic from causes other than hyperparathyroidism. In all six patients the concentration of serum calcium had been raised on several occasions for at least two years and no associated malignancy had been disclosed. We also studied 18 patients with hypertrophic cardiomyopathy diagnosed by echocardiography and, in some cases, angiography.

ECHOCARDIOGRAPHY

M mode echocardiograms were recorded with an Irex IIIB ultrasonoscope (frequency 2.25 MHz, repetition rate 1000/s). The output was displayed on a strip recorder at a paper speed of 100 mm/s with a simultaneous electrocardiogram. Records were taken with the patient in the left lateral position. Echocardiograms were recorded just above the level of the tips of the mitral valve cusps so that movement of the cusps could be observed. Care was taken to produce clear continuous endocardial echoes. Additional views were recorded to show the aortic and mitral valves. All procedures were performed by one observer (RAG) without knowledge of the patient's biochemical status. The following measurements

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Accepted for publication 5 August 1985

Table 1 Echocardiographic data (mean (1SD)) for 40 study patients

Variable	Hypercalcaemia					Hypertrophic cardiomyopathy (n = 18)
	Hyperparathyroidism (n = 16)				Normal* (n = 6)	
	NLV (n = 1)	SLVH (n = 6)	ASH (n = 4)	HCM (n = 5)		
LV posterior wall (mm)	10	17 (4)	9 (1)	15 (4)	10 (2)	14 (5)
LV septal thickness (mm)	10	17 (5)	19 (4)	22 (7)	11 (1)	20 (6)
LV septal:PW thickness ratio	1	1 (0.2)	2.2 (0.2)	1.5 (0.2)	1.2 (0.3)	1.5 (0.4)
LV End systolic dimension (mm)	28	24 (4)	25 (7)	21 (6)	30 (5)	23 (5)
Septum to mitral valve (mm) at onset of systole	28	23 (4)	26 (5)	21 (2)	26 (3)	22 (7)
SAM (%)	0	0	0	20	0	56
Premature AV closure (%)	0	0	0	20	0	11

*Normal parathyroid functions. NLV, normal left ventricular dimensions; SLVH, symmetric left ventricular hypertrophy; ASH, asymmetric septal hypertrophy; HCM, hypertrophic cardiomyopathy; LV, left ventricle; AV, aortic valve; SAM, systolic anterior motion of the mitral valve, PW, posterior wall.

were obtained over five cycles and a mean value was calculated: (a) End diastolic posterior wall thickness and septal thickness were estimated at the onset of the Q wave. A posterior wall thickness of >10.5 mm and a septal thickness of >11 mm at end diastole were regarded as abnormal as was a septal to posterior wall ratio of $>1.3:1$. (b) Left ventricular cavity dimension was estimated at end systole—that is the minimum dimension. (c) The distance from the endocardial surface of the septum to the mitral valve at the onset of systole was estimated. (d) The presence or absence of systolic anterior motion of the mitral valve and mid-systolic closure of the aortic valve were noted.

Echocardiograms were classified as normal, symmetric left ventricular hypertrophy, asymmetric hypertrophy, or hypertrophic cardiomyopathy according to the criteria of Gibson *et al*³ and Doi *et al*.⁴

None of the patients had clinical or echocardiographic evidence of valvar heart disease.

OTHER INVESTIGATIONS

Plasma calcium, phosphate, alkaline phosphatase, urea, electrolytes, and creatinine were measured on a SMAC Technician AutoAnalyzer. Serum parathyroid hormone concentration was measured by a

radioimmunoassay (Immunonuclear Co-operative Corporation, Stillwater, Minnesota, USA) with an antibody specific for the mid-molecular peptide of parathyroid hormone. In our hands the sensitivity of this assay is 10 pmol/l and intra-assay variation is less than 10%. This assay method is based on that described by Roos *et al*.⁵ The normal reference range for parathyroid hormone in our laboratory is 20–85 pmol/l. The biochemical results for this study were those recorded at the time of the diagnosis of each patient.

Results

In all patients with hypertrophic cardiomyopathy the posterior wall was ≥ 8 mm thick and the septum was ≥ 15 mm. Patients with symmetric left ventricular hypertrophy also had posterior wall and septal thickness greater than 13 mm. Patients with asymmetric septal hypertrophy had a posterior wall thickness greater than 7 mm but a septal thickness of greater than 12 mm. Table 1 gives details of all measurements.

Table 2 shows biochemical data for all 22 patients presenting with hypercalcaemia. There were two groups of patients: those in whom parathyroid hormone concentration was raised and those in whom it

Table 2 Biochemical data (mean (1SD)) in 22 patients presenting with hypercalcaemia

	Calcium (mmol/l)	Phosphate (mmol/l)	AP (IU/l)	PTH* (pmol/l)
Hypercalcaemic with raised PTH (n=16)				
Normal LV dimensions (n=1)	2.94	0.88	160	260
Hypertrophic cardiomyopathy (n=5)	2.96 (0.35)	0.89 (0.13)	110 (41)	220 (100–1000)
Asymmetric septal hypertrophy (n=4)	2.98 (0.15)	0.8 (0.25)	170 (110)	300 (160–420)
Symmetric LV hypertrophy (n=6)	2.97 (0.33)	0.79 (0.14)	110 (80)	320 (140–1000)
Hypercalcaemic with normal PTH concentration (n=6)	2.73 (0.09)	0.83 (0.08)	77 (26)	55 (40–70)

*Median (range). AP, alkaline phosphatase; LV, left ventricle; PTH, parathyroid hormone

Table 3 Biochemical data (mean (1SD)) in 18 patients presenting with hypertrophic cardiomyopathy

	Calcium (mmol/l)	Phosphate (mmol/l)	AP (IU/l)	PTH* (pmol/l)
Patients with normal PTH concentration (n=13)	2.43 (0.12)	1.07 (0.12)	74 (18)	50 (25–77)
Patients with raised PTH concentration (n=5)	2.37 (0.08)	1.14 (0.13)	94 (52)	135 (89–350)

*Median (range) AP, alkaline phosphatase, PTH, serum parathyroid hormone.

was normal.

Of 16 patients with primary hyperparathyroidism, five had hypertrophic cardiomyopathy, six had symmetric left ventricular hypertrophy, and four had asymmetric septal hypertrophy. One patient had no echocardiographic abnormalities. No echocardiographic abnormality was seen in any of the six hypercalcaemic patients without hyperparathyroidism.

Parathyroid hormone concentration was raised in five of the 18 patients with hypertrophic cardiomyopathy. None of the patients had hypercalcaemic, hyperphosphataemic, or renal failure to explain the increase in parathyroid hormone concentration (Table 3).

In patients with primary hyperparathyroidism, serum concentrations of calcium, phosphate, alkaline phosphatase, and parathyroid hormone were similar in those with hypertrophic cardiomyopathy, symmetric left ventricular hypertrophy, or asymmetric septal hypertrophy.

Discussion

Our data show that primary hyperparathyroidism is almost invariably associated with left ventricular hypertrophy in its various forms. Five of sixteen patients with hyperparathyroidism had hypertrophic cardiomyopathy. We found no echocardiographic evidence of myocardial hypertrophy in patients with hypercalcaemia due to causes other than primary hyperparathyroidism; all patients in this group had low or non-detectable serum concentrations of parathyroid hormone. McFarland *et al* have suggested that hypertrophic cardiomyopathy may be related to the prolonged stimulus provided by hypercalcaemia.⁶ From our study, it seems that myocardial hypertrophy (including hypertrophic cardiomyopathy) is primarily associated with parathyroid hormone itself and not with a raised concentration of extracellular calcium.

The high frequency of increased parathyroid hormone concentrations in patients who presented with clinical and echocardiographic features of hypertrophic cardiomyopathy, suggests an association between raised concentrations of this hormone and

hypertrophic disease. Five of 18 patients with hypertrophic cardiomyopathy had increased serum concentrations of parathyroid hormone with normal serum concentrations of calcium and phosphate and no renal failure. As far as is known, the mid-molecular assay is specific for parathyroid hormone but we cannot exclude the possibility that the immunoassay was detecting some similar but distinct peptide with a direct effect on cardiac muscle calcium flux. The high frequency of raised serum concentrations of parathyroid hormone in our patients with hypertrophic cardiomyopathy contrasts with the results of McFarland *et al* who found raised hormone concentrations in only two of 32 cases of hypertrophic cardiomyopathy.⁶ This difference may have been due to the different assays used in the two studies.

Parathyroid hormone has a positive chronotropic effect on myocardial cells in culture and its action is mimicked by calcium ionophore and blocked by verapamil.⁷ In hamsters with congenital myopathy there was an increase in intracellular calcium concentrations in skeletal muscle; after parathyroidectomy the intracellular calcium concentration fell and myopathy improved.⁸ Parathyroid hormone has also been shown to have a positive inotropic effect on the rat heart at physiological concentrations.⁹ Since this action is also blocked by verapamil, it must be directly related to the movement of calcium into the myocardial cell. These experimental data indicate that parathyroid hormone has a direct effect on the myocardium which is mediated by an influx of calcium. Such positive chronotropic and inotropic effects are consistent with the possibility that in the long term the maintenance of high concentrations of parathyroid hormone may result in cardiac hypertrophy. Hypertrophy and disarray of the cardiac muscle fibril, identical to that seen in hypertrophic cardiomyopathy, has been produced experimentally by substances which disturb membrane stability, such as triac and calcium ionophore,^{2,10} and parathyroid hormone could act in a similar way. The time that has elapsed since some of our patients had parathyroidectomy is not sufficient to assess whether myocardial hypertrophy has regressed. Clinical evidence suggests that

improvement will occur.¹¹ Experiments aimed at investigating the structure and function of the myocardium using a parathyroid hormone stimulus are underway in our laboratory and are designed to define both the mode of action of the hormone and to build a model of increasing ventricular hypertrophy.

Our data indicate that all patients with hyperparathyroidism should be examined by echocardiography so that the presence of myocardial hypertrophy will not be missed. Conversely, serum concentrations of parathyroid hormone should be measured in all patients with left ventricular hypertrophy from an unknown cause, (especially those with hypertrophic cardiomyopathy) so that any parathyroid abnormality can be treated. Most of our patients with raised serum parathyroid hormone concentrations had normal electrocardiograms and none was hypertensive. Females predominated in the present series and this may be because of the small numbers of patients studied.

In conclusion, an association between cardiac hypertrophy (symmetric, asymmetric, and hypertrophic cardiomyopathy) and an increased concentration of parathyroid hormone has been demonstrated that is independent of hypercalcaemia. For the first time a pattern of cardiac muscle hypertrophy clearly related to an hormonal abnormality has been shown to occur. This adds another dimension to the understanding of a possible cause of idiopathic ventricular hypertrophy and even suggests that hypertrophic cardiomyopathy could be one form of end stage exuberant cardiac muscle hypertrophy. Further elucidation of the role and nature of parathyroid hormone in relation to ventricular hypertrophy and of a causal link between hyperparathyroidism and all forms of ventricular hypertrophy, including hypertrophic cardiomyopathy, is awaited.

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Hypertrophic cardiomyopathy associated with a mitochondrial myopathy of voluntary muscles and congenital cataract

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SUMMARY Structurally abnormal mitochondria were found in skeletal muscle cells from a woman with hypertrophic cardiomyopathy and myopathy of voluntary muscles associated with congenital cataracts. Moderate exercise resulted in lactic acidosis. Oxidation of pyruvate and other substrates and the production of adenosine triphosphate were normal in vitro. A younger brother of the patient had had congenital cataract and had died from hypertrophic obstructive cardiomyopathy.

The concurrent occurrence of pathological changes in both heart and skeletal muscle is a feature of several inherited diseases such as Duchenne and Becker muscular dystrophies. The heart and voluntary muscles are also both affected in several diseases with a well defined enzyme deficiency, such as Pompe's disease, and in other diseases in which the molecular defect is unknown.

Ten years ago we described seven patients from three unrelated families who had hypertrophic cardiomyopathy and a mitochondrial myopathy of skeletal muscle.¹ They had associated symptoms of congenital cataracts and exercise related lactic acidosis. The syndrome is now registered as an inherited disease 21235 on the McKusick register.² Recently we had the opportunity to study two other patients from one family who had this syndrome. On this occasion we are able to perform biochemical studies on skeletal muscle tissue from one of the patients.

Case reports

PATIENT 1

This woman of 33 was the third of five children of healthy non-consanguineous parents. Within a few weeks of birth, bilateral cataracts were identified. These were surgically removed when she was 6 months old. She always became very tired during

exercise and she could never compete physically with her peers. At the age of 25 years she was first admitted to our hospital for cardiological examination because her brother had died from a cardiomyopathy. Her other sibs were healthy. She was known to have had a heart murmur for about 20 years. Her exercise tolerance worsened with activity, but did not change consistently with time of day, food intake, or menstrual cycle. She denied progression of her exercise intolerance, and also had no dysarthria, dysphagia, diplopia, muscle cramps, fasciculations, or myotonia. She did not drink alcohol to excess or take drugs, other than the occasional aspirin. General examination at the age of 33 years was unremarkable except for moderate obesity (height 160 cm, weight 50 kg). She was visually handicapped by aphakia. Her mental state, cranial nerve function, muscle bulk and tone, tendon reflexes, sensation, and coordination were normal. Muscle strength during individual movements was normal but her endurance was extremely limited. Cardiological examination showed cardiomegaly and a grade II systolic murmur at the left sternal border. Blood pressure was 120/70 mm Hg. There was electrocardiographic evidence of hypertrophy of the right and left ventricles (Fig. 1) and apical hypertrophic cardiomyopathy was diagnosed by echocardiography. The interventricular septum measured 16 mm and the posterior left ventricular wall 13 mm at the level of the mitral valve. The wall and septum were both 18 mm thick at the apex. Doppler studies did not show flow velocity abnormalities. During exercise testing on a bicycle ergometer she

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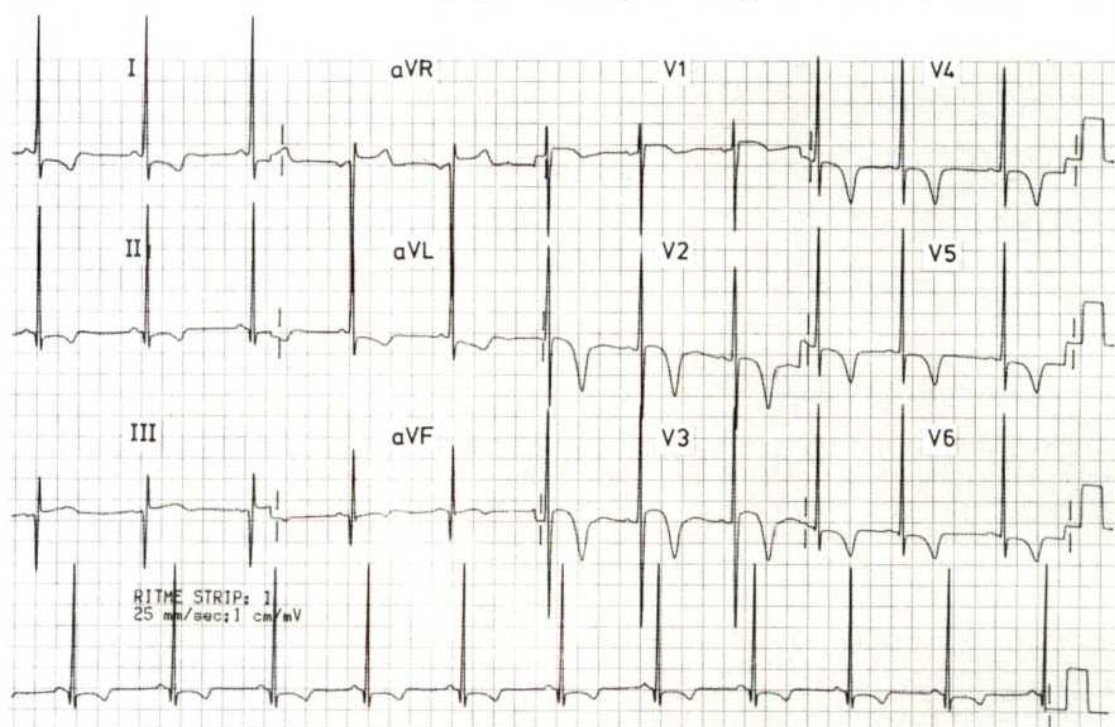


Fig. 1 Electrocardiogram in patient 1 showing evidence of hypertrophy of the right and left ventricles.

was not able to perform at the 40 W level for more than a few minutes before she became exhausted. Laboratory examination showed a normal arterial pH and lactic acid concentration at rest but a serious metabolic acidosis (pH, 7.28; bicarbonate 15.4 mmol/l; base excess, -9.9 mmol/l) and raised lactic acid concentration (10.4 mmol/l, normal <1.8 mmol/l) after submaximal exercise. Lactic acid concentration after 5 minutes' exercise on a treadmill at a speed of 2 miles per hour (3.2 km per hour) and an inclination of 10% increased by 3.6 mmol/l and pH fell from 7.37 to 7.22. (There were no changes in controls). Serum creatine kinase concentration was normal. Maximum heart rate was 140 beats per min. A specimen of the patient's quadriceps muscle was obtained by open biopsy after she had given informed consent.

PATIENT 2

A younger brother of patient 1 was admitted to our clinic at the age of 18 years with cardiomegaly. At the age of 5 years he also had had congenital cataracts removed. He suffered from exercise intolerance. General examination revealed no severe abnormalities. Blood pressure was 135/80 mm Hg. A chest x ray examination showed cardiomegaly and a grade II systolic murmur was heard at the left sternal border

and in the second right intercostal space. Hypertrophy of the left ventricle and of the interventricular septum was diagnosed by electrocardiography and vector cardiography. Heart catheterisation showed normal pressures. The tip of the catheter, however, could not be placed in the most distal part of the left ventricle. The cineangiographic findings were typical of hypertrophic obstructive cardiomyopathy. Subjectively he remained well until he was 23 years old when he was readmitted with an attack of cardiac asthma. He responded well to conventional treatment. Shortly afterwards, however, cardiac asthma developed again and he died. The most important finding at necropsy was myocardial hypertrophy. The heart weighed 1220 g. Hypertrophy of the septum and the left ventricle had seriously narrowed the outflow tract. The right ventricle was also hypertrophied. The heart valves were intact and there were no defects in the atrial or ventricular septa. The coronary arteries were normal.

HISTOPATHOLOGICAL EXAMINATION

Skeletal muscle

Muscle fibres from patient 1 did not vary greatly in size or shape. No necrotic fibres were seen and there was no inflammation. Connective tissue, nerve bundles, and blood vessels were normal. Haematoxylin

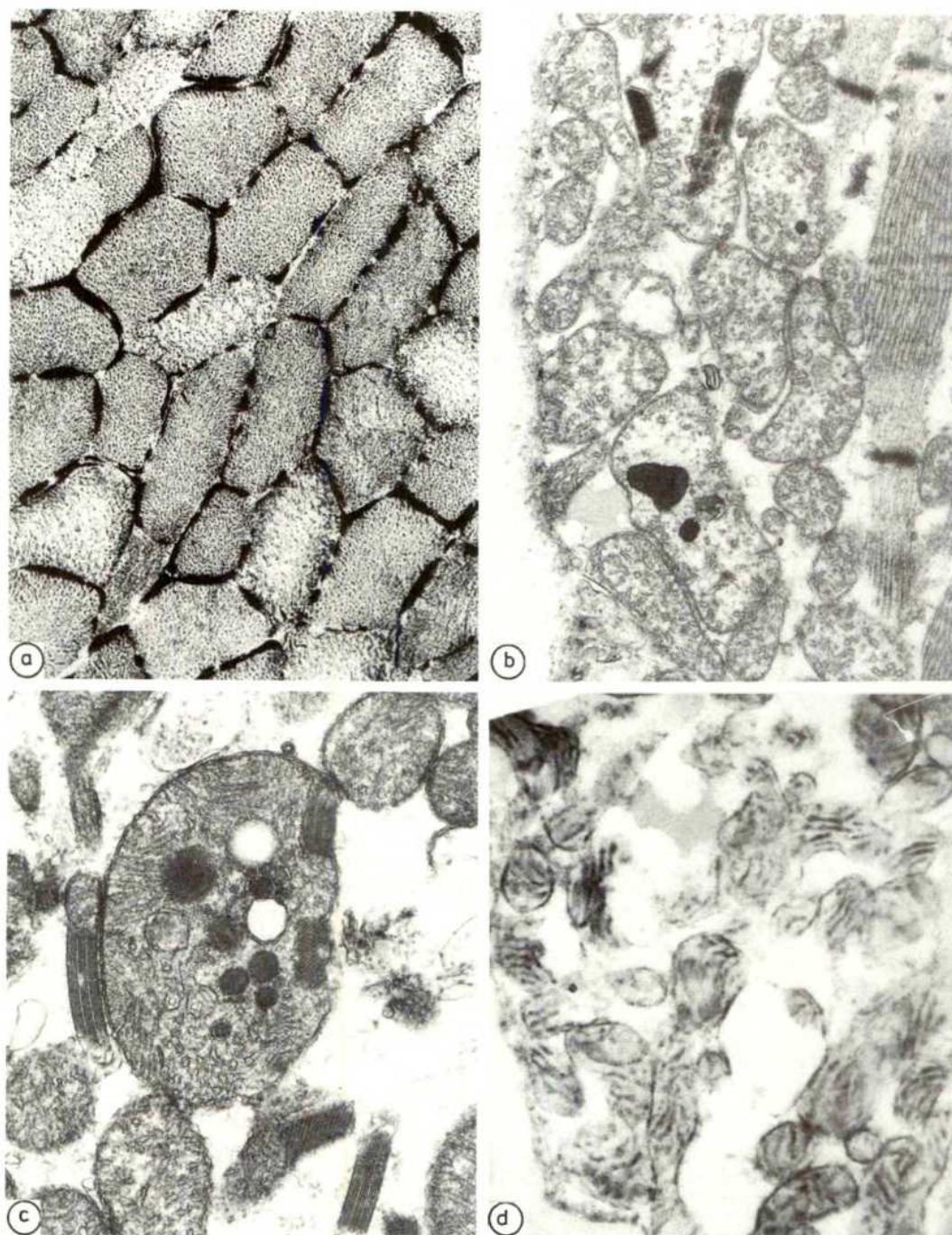


Fig. 2 Various mitochondrial abnormalities seen in a biopsy specimen of the quadriceps muscle from patient 1. (a) Low power photomicrograph of a transversely sectioned muscle fibre stained by means of the succinic dehydrogenase reaction to show the mitochondria. Note the strong staining of the subsarcolemmas of most muscle fibres. No ragged red fibres were seen. Original magnification, $\times 270$. (b) Low power electron micrograph of subsarcolemmal area showing poorly developed cristae in mitochondria and electron dense matrix deposits. Original magnification, $\times 22\,000$. (c) High power electron micrograph of giant mitochondrion with crystalline and amorphous inclusions. Original magnification, $\times 93\,000$. (d) Electronmicrograph showing histochemical reaction to cytochrome oxidase by aberrant subsarcolemmal mitochondria. Original magnification, $\times 18\,000$.

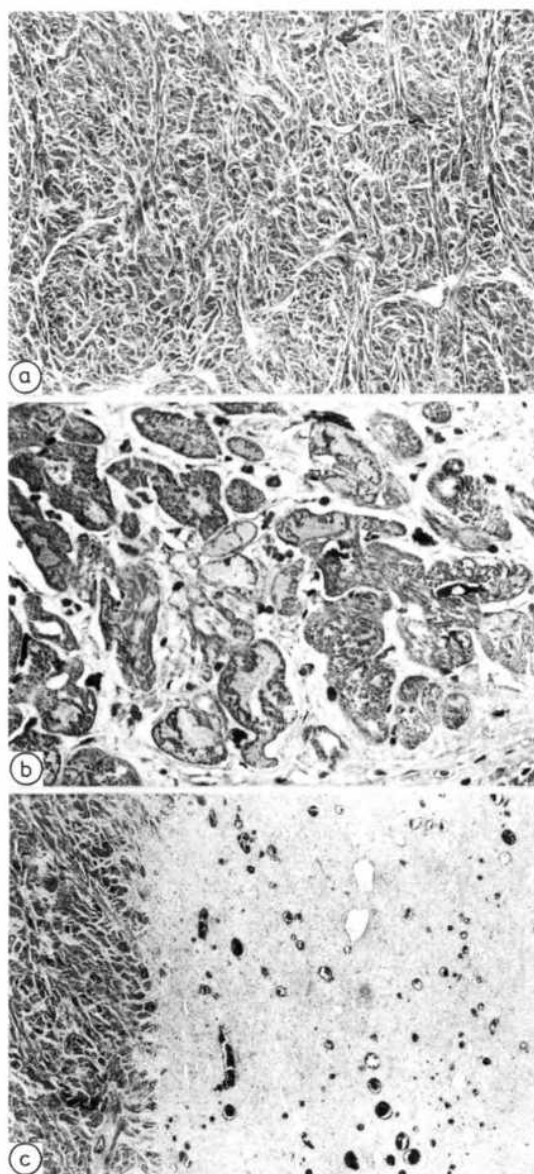


Fig. 3 Photomicrographs of myocardial fibres from patient 2. (a) Disarrayed myocardial fibres of type IIA and IIB (according to Maron⁴) in the septum. Elastin trichrome Masson stain. Original magnification, $\times 35$. (b) Myofibrillogenesis and vacuolar dystrophy of severely hypertrophic muscle fibres with pericellular fibrosis. These are small scars in left upper and lower corner. Elastin trichrome Masson stain. Original magnification, $\times 350$. (c) Laminar scar seen in the middle third of the ventricular septum. Elastin trichrome Masson stain. Original magnification, $\times 35$.

and eosin stained sections showed that most of the muscle fibres contained an increased amount of bluish red granular material in the subsarcolemmal regions. In preparations stained by the modified Gomori trichrome technique red granular material was seen beneath the sarcolemma in numerous fibres, but there were no distinct "ragged red" fibres.

The number of lipid droplets between the myofibrils and under the sarcolemmal membranes was increased. Periodic acid/Schiff staining showed that fibres with high lipid content also contained increased amounts of glycogen. There was no correlation, however, between lipid and glycogen storage and the intensity of the trichrome red staining. There was a slight predominance of type I adenosine triphosphatase reactions but in other respects a normal checkerboard pattern of the distribution of fibre types was seen. There was a pronounced increase in the amount of reaction product within individual fibres when succinic dehydrogenase and NADH-tetrazolium reductase were used to stain for mitochondria (Fig. 2a).

Electronmicroscopy showed a considerable disturbance of the contractile apparatus with dilatation of intermyofibrillar spaces, splitting of myofibrils, and loss of the concerted arrangement of sarcomeres in many muscle fibres. More serious, however, was the great increase in aberrant mitochondria. Many of the intermyofibrillar and subsarcolemmal mitochondria did not have cristae of normal appearance and arrangement. Also they often contained cristallike inclusions and osmiophilic deposits of variable size and density (Fig. 2b and c). Quantitative morphometric stereological studies³ (ratio(SE)) confirmed that there was a distinct increase in the volume density (volume fraction occupied by the component) of the mitochondrial compartment (8.46, normal 4.28 (1.84)) and of the lipid (1.79, normal 0.79 (0.50)) and glycogen (3.11, normal 1.19 (0.87)) deposits when compared with results in untrained age matched controls. Enzyme histochemistry showed normal activity of cytochrome oxidase (Fig. 2d). Unfortunately, no skeletal muscle from patient 2 was available for examination.

The heart (patient 2)

The myocardial fibres varied in size and shape and some were in considerable disarray (Fig. 3a) (type IIA and IIB by Maron and Roberts's classification⁴). Many of them contained vacuoles and showed myofibrillogenesis. There were multiple scattered small scars in the myocardium of the left ventricle (Fig. 3b), moreover a broad laminar fibrosis was found in the middle third of the septum (Fig. 3c), while the portions of the septum adjacent the right and left ventricle were spared. A small deparaffinised myo-

cardiac specimen was postfixed in glutaraldehyde and examined by electron microscopy. Despite artefacts due to paraffin embedding, myofibrils were clearly recognisable. There was a great increase in mitochondria throughout the myocardial fibres. The size of the mitochondria varied greatly, many contained large osmiophilic inclusions, apparently identical to those seen in the skeletal muscle mitochondria from patient 1.

Biochemical examination

Rates of pyruvate and malate oxidation in the muscle homogenate were assayed by the method of Bookelman *et al.*⁵ with the glucose hexokinase system being replaced by 20 mmol/l creatine. P^i, P^5 -di(adenosine-5'-)pentaphosphate (Ap5A) was added to inhibit adenylate kinase activity.⁶ Adenosine triphosphate production rates were determined in the presence of Ap5A and corrected for arsenite insensitivity.⁶ Cytochromes were assayed by the method of Bookelman *et al.*⁷ Carnitine was estimated by the method of Parvin and Pande.⁸

Biochemical examination did not show a clear cut defect in the energy producing pathway of the mitochondria. The cytochromes were present in normal amounts. Concentrations of total and non-esterified carnitine were normal in serum and muscle homogenates.

Discussion

Our patients and those described before¹ probably had a hereditary disease of heart and skeletal muscle associated with congenital cataracts. On the basis of pathophysiological criteria the cardiomyopathy can be classified as a hypertrophic cardiomyopathy. In the patient who died the gross pattern of the heart was characteristic of this type of cardiomyopathy. The broad scar in the septum, however, was an unusual finding. It can only be supposed that it developed because of a concurrent disturbance of coronary perfusion in the severely hypertrophic myocardium.

Pronounced changes in the ultrastructure and distribution of mitochondria in the myocardial and skeletal muscle fibres were the most prominent histopathological findings. There are several reports of mitochondrial abnormalities in the skeletal muscles of patients with a heart disease.⁹⁻¹¹

A functional abnormality is likely in patient 1 because there was abnormally high lactic acidosis after exercise as a consequence of impaired pyruvate oxidation. Biochemical examination of muscle tissue, however, excluded the well known causes of disordered pyruvate oxidation. A disturbance of oxygen delivery to the mitochondria might explain

the disordered mitochondrial function. Unfortunately we did not test for oxygen availability in vivo. Impaired oxygen delivery might also explain the occurrence of congenital cataract since the lens is vascularised for only a limited time during fetal development. Impaired oxygen delivery can cause cataract in experimental studies.¹²

Although we know of several patients with this syndrome in The Netherlands, no other cases have been described in published reports. We know of a few more Swiss patients with the syndrome (B Steinman, personal communication). The frequency of such cases is probably greater than the small number of reported cases suggests.

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Case report

Chylopericardium: a rare complication of a Waterston shunt

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SUMMARY A case of chylopericardium occurring after a Waterston shunt was successfully managed by pericardial drainage of chyle and substitution of dietary fats with medium chain triglycerides.

Chylous pleural effusion is a well recognised complication after thoracic surgery. The accumulation of chyle in the pericardium sufficient to cause tamponade, however, is a rare complication of cardiac surgery and was first described in 1971 by Thomas and McGoon.¹ The aetiology of chylopericardium is uncertain and because the condition is so rare the correct treatment has yet to be established. We report a case of this unusual complication in a 5 month old infant after a Waterston shunt and discuss the management of this condition.

Case report

A male infant weighing 1.8 kg was born at 33 weeks' gestation after the spontaneous onset of labour. He was small for dates, but there was nothing unusual in the antenatal history. Cyanosis was not clinically apparent, an electrocardiogram showed sinus rhythm with left ventricular dominance, and the chest x ray film showed an increased cardiothoracic ratio. A systolic murmur was heard and he was referred for assessment. Cardiac catheterisation showed pulmonary atresia with a hypoplastic right ventricle, widely patent ductus arteriosus, and a large atrial septal defect. As his condition was stable, surgical intervention was not warranted and he was discharged. He was readmitted at the age of five months because of failure to gain weight and mild cyanosis, and it was felt that a palliative shunt was required.

A standard Waterston shunt by the retrocaval

approach was carried out through a right lateral thoracotomy. The surgical procedure was uneventful and a good shunt murmur was audible after operation. The pleural drain was removed the following day. Two days later, however, an increase in heart size was noted on the chest x ray film; one week post-operatively the presence of a large pericardial effusion was confirmed by echocardiography but there were no specific features to suggest chylopericardium. Despite increased diuretic therapy the size of the effusion as assessed by echocardiography continued to increase.

Three weeks postoperatively surgical drainage was performed through a small sub-xiphoid incision; 200 ml of milky fluid was removed from the pericardium and a pericardial drain was left in situ. Laboratory analysis of the aspirated fluid showed the presence of chylomicrons and this confirmed the clinical diagnosis of chylopericardium. The patient was started on a diet in which dietary fats were replaced by medium chain triglyceride supplements. About 20 ml of chyle drained away each day for the next five days; drainage ceased after one week and the drain was removed. An echocardiogram two weeks later confirmed that no fluid had reaccumulated in the pericardium. Follow up three months later showed a heart of normal size on chest x ray film and normal echocardiographic appearance.

Discussion

The first case of chylopericardium after cardiac surgery was reported in 1971 by Thomas and McGoon.¹ Feteih *et al* reviewed nine further cases and added their own.² Since this review, further

Requests for reprints to Mr J R L Hamilton, FRCS, Department of Cardiac Surgery, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, Northern Ireland

cases have been added by Rose *et al*⁵ and Pugliese *et al*.⁴ These 13 cases span the full range of ages from infants to adults and cover the whole spectrum of cardiac operations from palliative shunts to definitive procedures.

Our case, like those reported by Hawker *et al*⁵ in 1972 and Jacob and colleagues⁶ in 1974, occurred in a patient who had had a Waterston shunt. The aetiology of chylopericardium after cardiac surgery is not clear but it seems that there is a definite risk of this complication after a Waterston shunt. Transection of an important lymphatic channel is obviously a factor, but such an event has only been described occasionally, despite the high frequency of anatomical variations in the course of the thoracic duct. In the case described by Thomas and McGoon, thrombosis of the left subclavian vein secondary to insertion of an external jugular vein cannula was described and they believed that this thrombosis had obstructed the end of the thoracic duct and produced high lymphatic pressures.¹ A similar aetiology was possible in the case described by Kansu *et al*⁷ and Rose *et al*⁵; however, in our patient venous access was maintained by a right internal jugular cannula.

The interval from operation to appearance of the chylopericardium ranges from four days, as in our case, to five weeks.⁵ This suggests that the aetiological development of the condition depends on whether damage to the major pericardial lymphatic occurs at operation or is a result of later fibrosis. Those who have reported cases of chylopericardium have not agreed on the management of such patients. Providing that no major lymphatic vessel had been damaged, as shown by excessive pericardial drainage or rapid reaccumulation of chyle after aspiration, most cases settled with conservative management. Adequate drainage of the pericardium is essential and this is most effectively

established by the insertion of a pericardial drain via the sub-xiphoid approach. Chyle formation can be reduced by controlling the dietary intake of fats. Fats are hydrolysed in the gut to glycerol and fatty acids and these long chain fatty acids are re-esterified to triglycerides and passed into the lymphatics as chylomicra. Medium chain triglycerides, however, are not re-esterified but pass directly into the portal venous blood. Thus the substitution of dietary fats with medium chain triglycerides is an effective method of reducing chyle formation, and this approach was successful in our case and that of others.

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Correspondence

Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia

Sir,

In their recent paper (1985; 53: 412-6) McKenna *et al* conclude that amiodarone may prevent sudden death in patients with hypertrophic cardiomyopathy. They studied patients with ventricular tachycardia recorded on Holter monitoring. Of 24 patients not treated with amiodarone (historical controls) five died suddenly during a three year follow up while all 21 patients on amiodarone survived for at least three years. The implications of this observation make careful examination of potential confounding factors essential. Information is required about the control group that is not explicit in the paper nor in a previous report about these patients.¹

The crucial issue is the drug treatment with "conventional antiarrhythmic agent" and the relation between the use of individual drugs and sudden death. McKenna *et al* state that "we entered seven of the patients with ventricular tachycardia (included in the conventional treatment groups) into a comparative study of the antiarrhythmic effect of disopyramide and mexiletine" ... "four of the seven died suddenly during treatment". Apart from this group there was therefore only one sudden death in the other 17 patients with ventricular tachycardia. Were these 17 also treated with mexiletine or disopyramide or just with quinidine, and how were the seven selected for the antiarrhythmic study? That these deaths were not typical of the natural history of hypertrophic cardiomyopathy is suggested in the earlier paper by the greater ages of these patients and they imply a more severe functional limitation than was found in 32 patients who died in the total series. Could it be that these older, more severely affected patients are particularly at risk from electrophysiological or mechanical instability when a particular antiarrhythmic agent is added to high dose beta blockade? This risk would not necessarily be marked by observable QT prolongation or premonitory arrhythmia.

On the data given by McKenna *et al* it could be concluded that mexiletine or disopyramide was responsible for most of the observed mortality and that the main benefit of amiodarone was in saving patients from being subjected to the toxic effects of these agents.

To clarify the situation it would be helpful to know what drugs each patient who died was taking (and for how long), the numbers of the survivors treated with similar drugs or combinations, and in which patients treatment was apparently successful (that is, did any of these patients die?). McKenna *et al* may also be able to supply from their own extensive experience or from elsewhere a more valid group for comparison with the amiodarone group—namely patients with hypertrophic cardiomyopathy and ventricular tachycardia who were not treated with antiarrhythmic agents but were treated with adequate beta blockade. Alternatively they could attempt to show that the overall three year mortality associated with the policy of amiodarone treatment of ventricular tachycardia is significantly different from that associated with treatment only by beta blocking or calcium antagonists drugs. Until this can be done their assertion that "a randomised prospective study" ... "was never feasible" is only justified in relation to comparison with the other antiarrhythmic agents. Long term treatment with amiodarone is not a trivial intervention and before it is applied to all patients with hypertrophic cardiomyopathy and ventricular tachycardias (except for relief of severe symptoms) a properly designed placebo controlled trial must be undertaken.

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Reference

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This letter was shown to Dr McKenna, who replies as follows:

Sir,

In his letter Dr Crick raises the possibility that the class I antiarrhythmic agents used in the treatment of 24 consecutive patients with hypertrophic cardio-

myopathy and ventricular tachycardia may have adversely affected prognosis.¹ The available evidence does not suggest this, but the possibility cannot be excluded. The arrhythmogenic effects of disopyramide, mexiletine, and quinidine are well known; 22 of the 24 patients had 12 lead electrocardiograms and 48 hour ambulatory electrocardiographic monitoring performed during treatment and we did not see changes that suggested an arrhythmogenic effect such as elongation of the QT interval or multifocal ventricular tachycardia. In this regard our data are similar to those reported by Maron *et al* for a study in which four of 19 patients who were receiving class I antiarrhythmic agents for the treatment of asymptomatic paroxysmal ventricular tachycardia died suddenly² without evidence of an arrhythmogenic effect of treatment (B J Maron, personal communication). Of the five patients with ventricular tachycardia who died suddenly in our study, three were on disopyramide (400 or 600 mg daily), one was on quinidine (500 mg daily), and the other had been treated with disopyramide and mexiletine (both were poorly tolerated) but was not on antiarrhythmic agents when death occurred. All of the survivors who had ventricular tachycardia received at least one class I antiarrhythmic agent. (These agents were never used in combination.) The drugs were changed according to their efficacy and side effects. The drug which was used for the longest period was disopyramide in 10, quinidine in eight, and mexiletine in four.

Before the recognition of asymptomatic ventricular arrhythmia and the use of class I antiarrhythmic agents, the annual mortality from sudden death in adults with hypertrophic cardiomyopathy was 2.6% (254 patients).³ Details of these patients have been published; in brief, the majority received propranolol (mean 220 mg daily) and few were on specifically antiarrhythmic drugs, usually for control of symptomatic supraventricular arrhythmia.³ With the widespread use of ambulatory electrocardiographic monitoring the high frequency of asymptomatic ventricular arrhythmia was recognised.^{4,5} During the period (1977 to 1980) when class I antiarrhythmic agents were used to treat paroxysmal ventricular tachycardia the overall annual mortality from sudden death was reported to be 2.7% (86 patients)⁵ and 2.4% (83 patients).² In these two predominantly adult populations the finding of ventricular tachycardia during electrocardiographic monitoring was associated with sudden death. The similar annual mortality before and after the treatment of ventricular tachycardia with class I antiarrhythmic agents does not support the suggestion of an occult arrhythmogenic effect.

Since 1980 we have routinely used amiodarone to

treat refractory supraventricular arrhythmia and paroxysmal non-sustained ventricular tachycardia. Our experience in the first 82 patients is outlined in our paper; the annual mortality from sudden death was 0.8%.¹ During the entire period under examination we used the same approach to treat symptoms, and the clinical, echocardiographic, and haemodynamic characteristics of the two consecutive patient populations were similar. These data on annual mortality do not suggest an adverse effect on prognosis by class I antiarrhythmic agents and they support the finding of improved survival during amiodarone treatment of patients with hypertrophic cardiomyopathy and ventricular tachycardia. We are well aware that long term treatment with amiodarone is associated with side effects, some of which are serious.⁶ For this reason we have been hesitant to assess the effect of amiodarone on sudden death in children with hypertrophic cardiomyopathy. This age group is at greatest risk of sudden death.⁷

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Reoperation for angina after previous aortocoronary bypass surgery

Sir,

The review paper by Pidgeon *et al* (1985; 53: 269–75) raises several points. Firstly, single vein grafts represented a high number of the patients undergoing both first and second operations, and recent reports have shown a pronounced increased frequency of perioperative spasm in just this group of patients¹—even to the extent of producing perioperative infarction—particularly in the non-grafted, often normal vessel. Was the occurrence of the 20 perioperative infarctions in this study higher in patients undergoing one or two vein grafts?

Secondly, the reasons for reoperation in this group were determined at angiography, although the relation between symptoms and the number and degree of coronary stenosis is clearly not linear.² Have the authors considered whether dynamic causes such as coronary vasospasm might play a more dominant role in the production of symptoms severe enough to require reoperation? Vasospasm may continue to affect host and graft vessels³ and is strongly implicated in the day to day variability experienced by nearly all patients with angina.⁴

Thirdly, many careful studies have already confirmed the lack of relation between traditional risk factors and progression of disease after coronary artery bypass graft.⁵ The persistence of type A behaviour (especially hostility, cynicism, and vocal stylistics) has been found to be significantly correlated with the development of postoperative angina,⁶ probably due to repeated and excessive sympathoadrenal medullary response to environmental stressors.⁷ Certainly, behavioural factors have been found to correlate very strongly with symptoms in men awaiting their first coronary artery bypass graft. Sleep disturbance (waking fatigued, poor quality sleep, long sleep latency) was found to contribute significantly to exertional, emotional, and post-prandial angina, whereas denial of helplessness and general life dissatisfaction correlated highly with rest and nocturnal angina.⁸

Of the patients in this study, 43% continued to have the same or worse anginal pain after the second operation, and the survey of published results suggests that this is not an uncommon problem. We would therefore direct the authors' attention to the role of dynamic factors in these patients and the suggestion that the best correlates are bio-behavioural. We have long advocated attention to

sleep (with sedation) and arousal (by counselling) in patients with angina⁹ as well as avoidance of hyperventilation, which may be the trigger to vasospasm.¹⁰

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This letter was shown to Dr Pidgeon, who replies as follows:

Sir,

In our series perioperative myocardial infarction occurred during the first operation in seven patients receiving three vein grafts, four receiving two grafts, and in only one who received a single graft. At reoperation seven of the eight infarcts occurred in patients with three vessel disease. In the Coronary Artery Surgery Study report the incidence of perioperative infarction increased with the number of grafts placed from 2.1% for single grafts to 6.3% for triple grafts.¹ Zingone *et al* report only one case of perioperative infarction in the territory subtended by a normal vessel and cited evidence of a further 11 cases.² We suspect, therefore, that this is not a frequent problem.

With regard to Drs Freeman and Nixon's second comment, all our patients suffered angina provoked by exertion or stress. This would suggest that the fixed obstructive lesions documented at coronary angiography, and confirmed at surgery, were likely to be responsible for their symptoms. In addition, some patients also reported angina at rest, whose genesis may be mediated by the same mechanism.³ Moreover, we assessed the severity of symptoms over a prolonged period, usually at least several months, thus circumventing the problem of day to day variability in symptoms. As we stated, symptoms are by definition subjective, although exercise testing is recognised to provoke evidence of ischaemia more readily in the presence of severe disease, both in the native⁴ and postoperative⁵ coronary circulation. For this reason we used exercise testing in many patients to aid selection for further investigation. We described the causes of postoperative angina as putative, based on an analysis of the angiograms, from which we determined the feasibility of surgery. The reason for reoperation, however, was to attempt to alleviate severe symptoms.

We noted a high incidence of conventional risk factors in our patients proceeding to reoperation, as do other authors.⁶ Anxiety may provoke angina, and the mechanism for this may be mediated by an increased myocardial oxygen demand.⁷ Although this aspect of the problem may be susceptible to modification of behaviour, our patients were so grossly restricted in terms of physical activity, despite medication, that we considered that coming to terms with their disability offered an inadequate solution. For patients whose disease was deemed inoperable there was no alternative.

We do not deny the role of dynamic and behavioural factors in the genesis of angina, but we question how far they are relevant in this group of patients with significant multivessel fixed obstructive lesions who have symptoms often despite vasodilator treatment. Our experience is that the relief of obstruction by further bypass grafts can produce symptomatic benefit in the majority.

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Lead specificity of the maximum ST/heart rate slope response

Sir,

Once more correspondence columns have borne witness to the confusion caused by the Leeds exercise test. Yet again Professor Linden and his colleagues have been able to claim that their protocol has not been adhered to—and of course on this occasion they are correct in that respect.^{1,2} They have, however, chosen to ignore other studies that have followed their protocol meticulously and that have, nevertheless, failed to reproduce their results.^{3,4}

This has surely now reached a point for real concern to be expressed. A considerable amount of time and money, much of the latter from charitable sources, has been spent trying to confirm the perfect accuracy of this test and this has proved a wild goose chase. This might be a cause for some amusement were the competition for scarce research funds not so intense. Nevertheless, the alleged usefulness of this test has been widely and uncritically accepted in many countries. There is reason to believe that the management of many patients may have been largely determined by the result of a Leeds exercise test, and of course this could well result in quite inappropriate decisions with regard to further investigation and treatment in individual cases.

The fact is that the test works only in Leeds. Nobody else, using the unmodified Leeds protocol, has been able to reproduce the results, and surely there-

fore the test must now either be abandoned or else all patients undergoing it must be sent to Professor Linden's unit since that would appear to be the only place where it can be properly performed and interpreted.

It is of interest that the recent letter from Professor Linden and Dr Mary seems to indicate that the test, even in Leeds, is no longer perfect so perhaps the time has come for it to be abandoned.

Clive Layton,
London Chest Hospital,
Bonner Road,
London E2 9JX.

References

- 1 Beatne JM, Seibert GB, Blomqvist CG. Lead specificity of the maximum ST/heart rate slope response [Letter]. *Br Heart J* 1985; 53: 349.
- 2 Linden RJ, Mary DASG. Lead specificity of the maximum ST/heart rate slope response [Letter]. *Br Heart J* 1985; 53: 688.
- 3 Balcon R, Brooks N, Layton C. Correlation of heart rate ST slope and coronary angiographic findings. *Br Heart J* 1984; 52: 304-7.
- 4 Quyyumi AA, Raphael MJ, Wright C, Bealing L, Fox KM. Inability of the ST segment/heart rate slope to predict accurately the severity of coronary artery disease. *Br Heart J* 1984; 51: 395-8.

Management of primary pulmonary hypertension

Sir,

Dr Oakley's interesting editorial on the management of primary pulmonary hypertension (*Br Heart J* 1985; 53: 1-4) contains an error. The sequence of the vascular lesions that is described ends with fibrinoid necrosis and the "plexiform arteriopathy" of Wagenvoort and Dr Oakley goes on to say "but the therapeutic dilemma is how to get hold of patients at a stage of medial hypertrophy before these irreversible changes occur." Plexiform lesions develop after fibrinoid necrosis. "Plexiform arteriopathy" does not exist. The term, plexogenic arteriopathy was devised by a World Health Organisation committee¹ to describe a morphological pattern of which the plexiform lesion is the final stage. There-

fore, plexiform lesions and other irreversible changes need not to be present in plexogenic arteriopathy. The condition, at least in association with congenital heart disease, is reversible in its early stages and not only when medial hypertrophy alone is present.² The primary form of plexogenic arteriopathy is also likely to be reversible if an effective treatment can be used at an early stage of disease.

C A Wagenvoort,
Department of Pathology,
Academisch Medisch Centrum,
Meibergdreef 9,
AZ Amsterdam,
The Netherlands.

References

- 1 Hatano S, Strasser T. *Primary pulmonary hypertension. Report of a WHO meeting*. Geneva: World Health Organization, 1975: 14-16
- 2 Wagenvoort CA, Wagenvoort N, Draulans-Noe Y. Reversibility of plexogenic pulmonary arteriopathy following banding of the pulmonary artery. *J Thorac Cardiovasc Surg* 1984; 87: 876-86

This letter was shown to the author, who replies as follows:

Sir,

I am grateful to Professor Wagenvoort for his semantic correction. "Plexogenic" presumably means giving rise to "plexiform". If only the arteriopathy

were "plexogenic" rather than "plexiform" when these patients are referred then we might produce some therapeutic benefit with vasodilator drugs. Very occasionally death from primary pulmonary hypertension occurs when the arteriopathy is still only "plexogenic" and one feels that in these rare patients the disease might have been amenable to treatment. We need to see patients when their arteriopathy although apparently "plexogenic" is not yet "plexiform".

Celia M Oakley,
Royal Postgraduate Medical School,
Hammersmith Hospital,
Ducane Road,
London W12 0HS.

Cardiac transplantation

Sir,

I was interested to read the letter in which Dr Evans (1985; 53: 472) compared the survival statistics of the Stanford University Cardiac Transplantation Program with the survival rates of medically treated patients with dilated cardiomyopathy in the United Kingdom. Dr Evans states that medical treatment of dilated cardiomyopathy carries a one year mortality rate of 34.7% and five year mortality rate of 59.4%. He compares this with the 37% one year mortality rate and a 61% five year mortality rate at Stanford. He then takes exception to the statement "that cardiac transplantation prolongs life". Fortunately, the current data upon which we base our justification for cardiac transplantation in the United States do not agree with Dr Evans's contention for several reasons.

The first and foremost criterion for cardiac transplantation in the United States is the presence of New York Heart Association class IV heart failure. In patients with class IV congestive heart failure, including those with coronary artery disease, one year mortality is 50% and three year mortality is 80%.¹ Since the quoted Stanford data include both patients with ischaemic heart disease and primary dilated cardiomyopathy the data do indeed appear promising. The Stanford statistics quoted comprise data accumulated before the introduction of cyclosporin immunosuppression. Comparison of one year and three year mortality rates in the registry maintained by the International Society for Heart Transplantation,² shows a 15% one year mortality

rate and a 25% three year mortality rate in patients who have had cardiac transplantation and immunosuppression with cyclosporin. Therefore, the most recent data indicate that cardiac transplantation does indeed prolong survival in those patients with New York Heart Association class IV heart failure. The problem in 1985 is not one of the therapeutic efficacy or of satisfactory long term immunosuppression but rather that of donor heart availability. The efforts of the medical community must be directed towards reducing the high early mortality rate of patients who presently are not surviving long enough to undergo cardiac transplantation.

Michael L Hess,
Director of Cardiac Transplantation,
Medical College of Virginia,
Richmond, VA 23298,
USA.

References

- 1 Califf RM, Bounous P, Harrell FE, *et al.* The prognosis in the presence of coronary artery disease. In: Braunwald E, Mock MB, Watson JT, eds. *Congestive heart failure and current research and clinical applications*. New York: Grune and Stratton, 1982. 31-40.
- 2 Kaye MP, Elcombe SA, O'Fallon WM. The International Heart Transplantation Registry: the 1984 report. *J Heart Transplant* 1985; 3: 290-2

Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 26 to 28 November 1985, and the closing date for receipt of abstracts was 1 August 1985.

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts will be 2 January 1986.

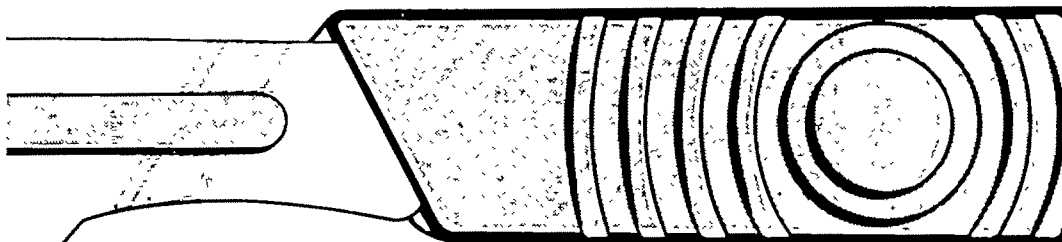
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ago. In future authors should take great care to check at source any reference they cite, or confirm references previously filed by using Index Medicus rather than the published work of another author, which may perpetuate errors.

Ventricular tachycardias

An international symposium on ventricular tachycardias will be held in Vittel, France, on 4 to 7 May 1986, under the auspices of the French Society of Cardiology. Inquiries to Professor J M Gilgenkrantz, Service de Cardiologie, Hôpital Central, 29 avenue du Maréchal-de-Lattre-de Tassigny, C O no 34, 54037 Nancy Cedex, France.



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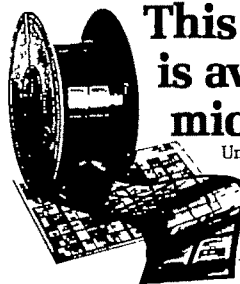
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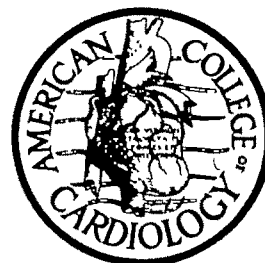
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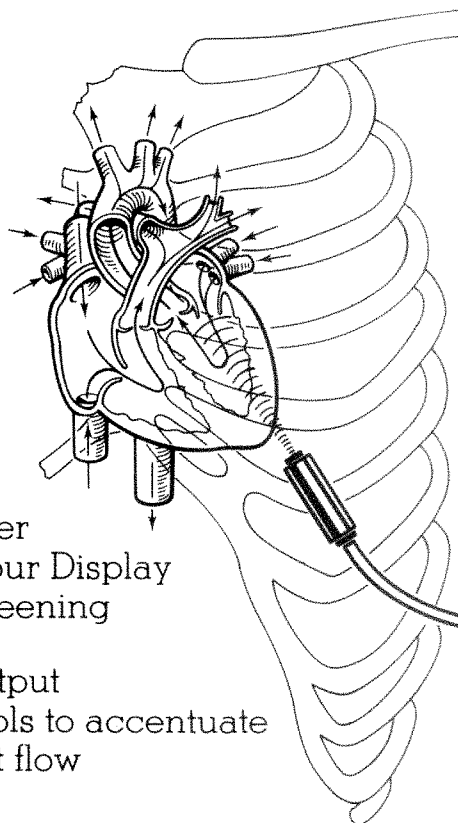
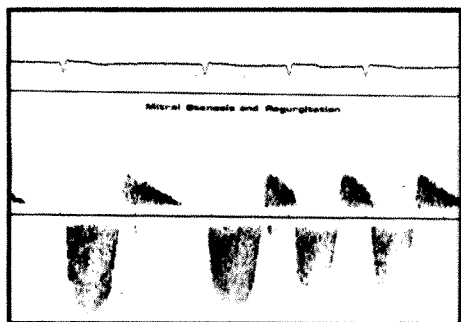
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CONTRA-INDICATIONS

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Effects of myocardial revascularisation in patients
with effort angina and those with effort and
nocturnal angina *A A Quyyumi, C A Wright,
L J Mockus, M Yacoub, K M Fox*

557

Doppler echocardiographic measurement of
flow velocity in the ascending aorta during supine
and upright exercise *P J Daley, K B Sagar,
L S Wann*

562

Sinus node sequences after atrial stimulation:
similarities of effects of different methods
W F Heddle, M E Jones, A M Tonkin

568

Preoperative and postoperative pulmonary function
tests in patients with atrial septal defect and their
relation to pulmonary artery pressure and
pulmonary:systemic flow ratio *P M Schofield,
P V Barber, T Kingston*

577

Congenital heart malformations in the first year of
life—a necropsy study *A S Hegerty,
R H Anderson, S Y Ho*

583

Subpulmonary pleural effusions in children after
cardiac surgery *C O'Callaghan, J Cooke, I H Kerr,
E A Shinebourne*

593

The heart and tuberous sclerosis: an
echocardiographic and electrocardiographic
study *J L Gibbs*

596

Case reports

Atrioventricular and sinoatrial block in thyrotoxic
crisis *M R Kramer, S Shilo, C Hershko*

600

Myocardial tuberculoma with rupture and
pseudoaneurysm formation—successful surgical
treatment *M A Halim, E N Mercer, G A Guinn*

603

Efficacy of an implanted automatic defibrillator
which had induced atrial fibrillation
L Jordaens, R Hamerlynck, D L Clement

605

Proceedings of the British Cardiac Society

609

Correspondence

657

Notices

659

Index

660

British Medical Association



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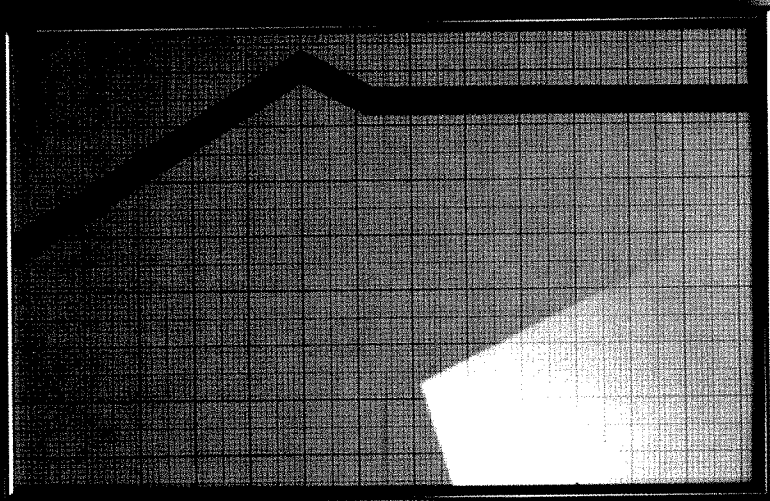
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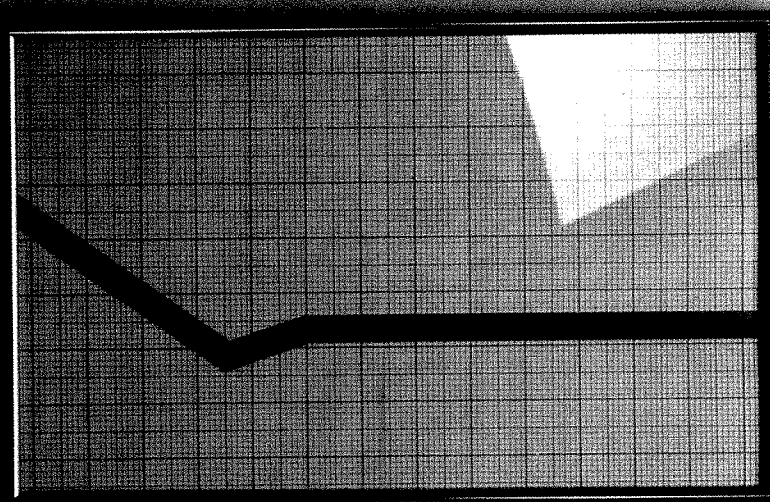


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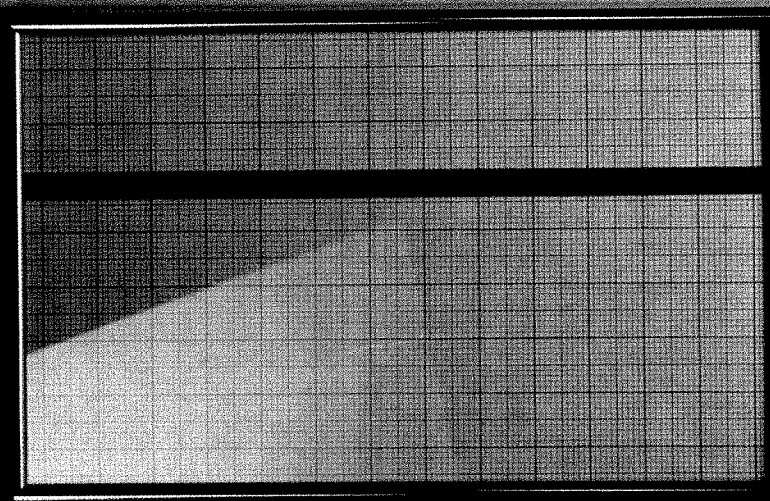
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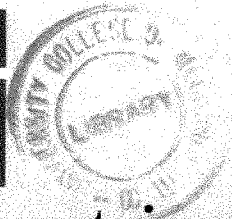
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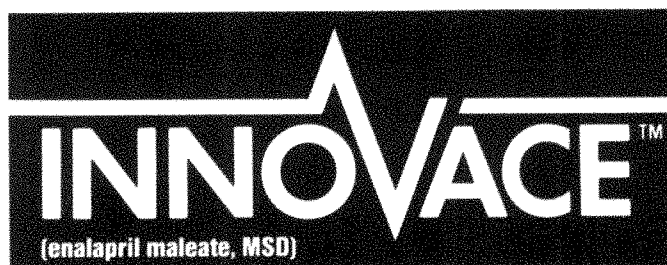
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CONTRA-INDICATIONS

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Hypersensitivity.

PRECAUTIONS

Symptomatic hypotension rarely after initial dose. More likely following volume depletion caused by prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhoea, or vomiting. Blood pressure may drop in some patients with congestive heart failure who have normal or low blood pressure.

Impaired renal function: Patients with renal insufficiency may require reduced or less frequent doses of 'Innovace' and their renal function should be closely monitored. In the majority, renal function will not alter, or may improve. Some hypertensive patients, with no apparent pre-existing renal disease, have developed minor and usually transient increases in blood urea and creatinine when 'Innovace' given concurrently with a diuretic. Dosage reduction of 'Innovace' and/or discontinuation of the diuretic may be required.

Renovascular hypertension: 'Innovace' can be used when surgery is not indicated, or prior to surgery. In some patients with bilateral renal artery stenosis or stenosis of the artery to a solitary kidney, increases of blood urea and creatinine, reversible upon discontinuation of therapy, have been seen. This is especially likely in patients with renal insufficiency. 'Innovace' is dialysable.

Because it is not known whether 'Innovace' is excreted in human milk, caution required if given to nursing mothers. Has not been studied in children.

DRUG INTERACTIONS

Increased antihypertensive effect when combined with methyldopa, β -blockers, and diuretics. Add ganglionic- or adrenergic-blocking drugs with caution. Plasma potassium usually remains within normal limits. If 'Innovace' is given with a diuretic, diuretic-induced hypokalaemia may be ameliorated. 'Innovace' may elevate plasma potassium levels in patients with renal failure. Potassium supplements or potassium-sparing diuretics should be given with caution, particularly in patients with impaired renal function, since they may lead to significant increases in plasma potassium. Lithium levels may be increased.

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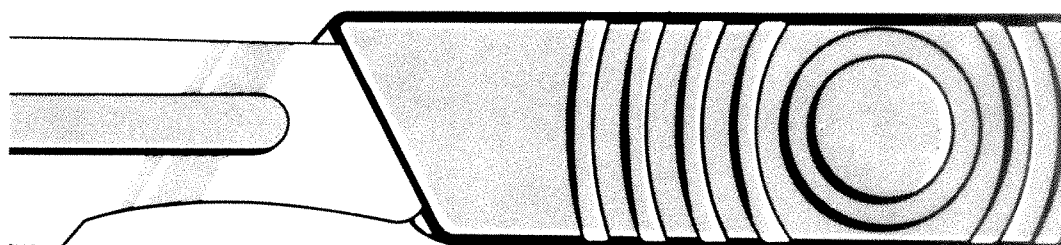
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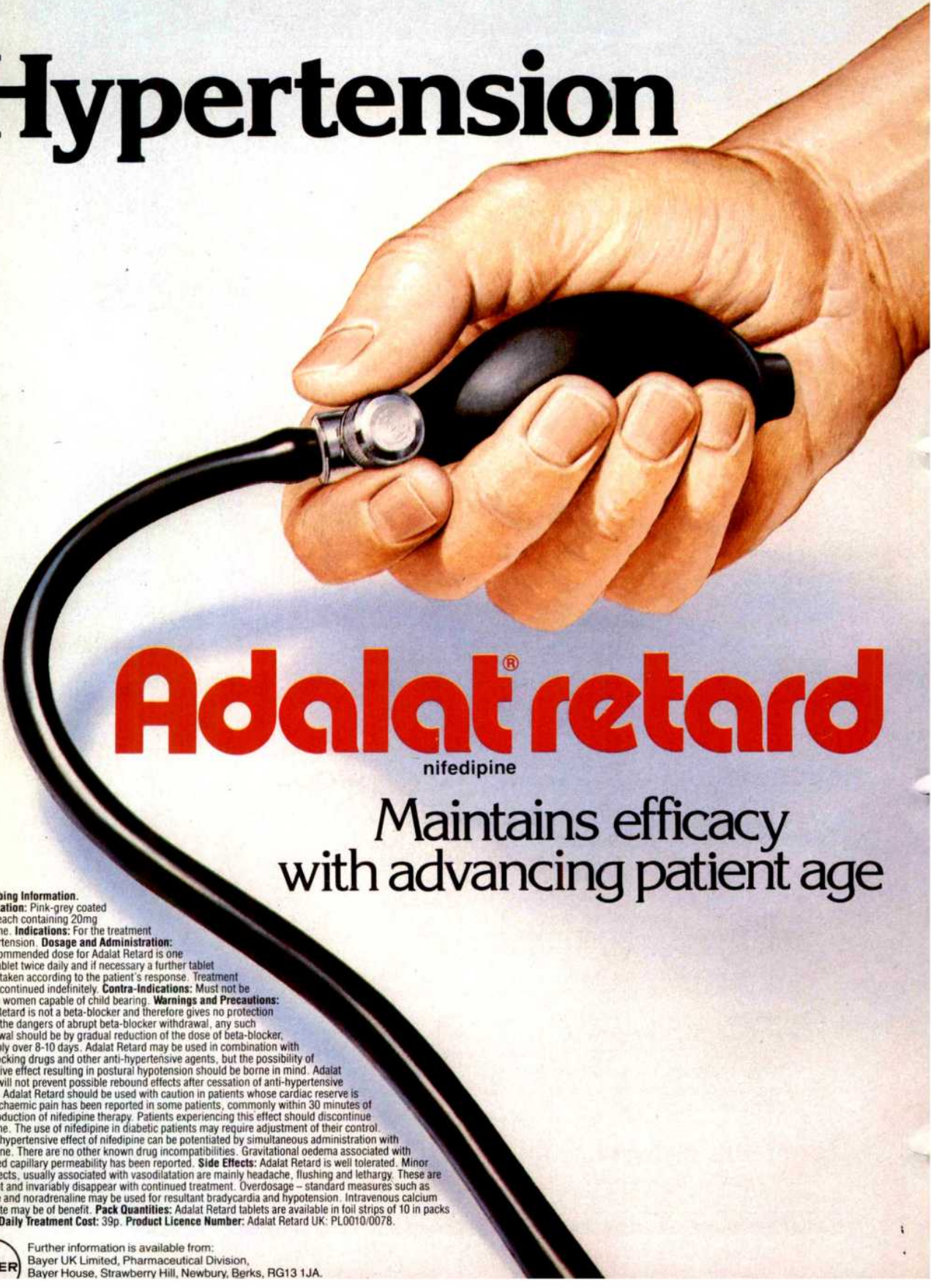
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Effects of myocardial revascularisation in patients with effort angina and those with effort and nocturnal angina

ARSHED A QUYYUMI, CHRISTINE A WRIGHT, LORNA J MOCKUS,
MAGDI YACoub, KIM M FOX

From the National Heart Hospital, London

SUMMARY The effects of coronary artery bypass graft operation were studied in 32 patients with daytime ambulatory ST segment changes and 14 patients with daytime and nocturnal angina and ST segment changes. Patients had ambulatory ST segment monitoring and exercise testing before and after operation and coronary arteriography was repeated in 34 patients after operation. Before operation, patients with daytime and nocturnal ischaemia tended to have more severe coronary artery disease, lower exercise tolerance, and more frequent ambulatory ST segment changes than those who had daytime ST segment changes only. After operation chest pain recurred in 22% of patients and ST segment depression during exercise testing or ambulatory ST segment monitoring recurred in 37% of the patients and was significantly more frequent in those with nocturnal ischaemia than in those with daytime ischaemia. Graft patency rates were similar in patients with and those without recurrence of ischaemia. After operation the frequency and magnitude of ST segment changes and exercise duration were improved in patients with preoperative daytime angina and also in those with daytime and nocturnal angina. The improvement was more pronounced in the latter groups. Thus, absence of postoperative angina is not a reliable indicator of the absence of reversible myocardial ischaemia. After revascularisation, patients with rest and nocturnal angina can expect relief from ischaemia, and if this recurs postoperatively, the threshold is improved and pain usually occurs only on exertion.

Several studies have demonstrated the efficacy of coronary artery bypass surgery in relieving symptoms in patients with obstructive coronary artery disease¹⁻³ and exertional angina when myocardial oxygen demand exceeds supply. Revascularisation in these patients improves exercise capacity^{6,7} and left ventricular function.⁸ Several pathophysiological mechanisms have been proposed to explain the occurrence of angina at rest and at night. These include an increase in myocardial oxygen demand,⁹ coronary spasm,¹⁰ and platelet aggregation.¹¹ The benefits of revascularisation in these patients have not been established.¹² We have investigated the value of coronary artery bypass surgery in patients with nocturnal rest angina and have compared these effects with those in patients with daytime exertional angina only.

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Accepted for publication 21 August 1985

Patients and methods

PATIENTS

Forty four of the 46 patients studied had episodes of transient ST segment depression and two had episodes of ST segment depression and elevation during preoperative ambulatory ST segment monitoring. These patients were selected from 100 consecutive patients who had coronary artery bypass surgery between 1982 and 1984 and who were under the care of one consultant cardiologist at the National Heart Hospital. Only patients with episodes of transient ST segment changes before operation were investigated before and after coronary artery bypass surgery. There were 37 men and nine women (mean (SD) age (57 (8) years). Thirty two patients (group 1) only had ST segment changes during daytime exertion and 14 (group 2) had both daytime and nocturnal ST segment changes. In twenty three patients antianginal medication was discontinued for the performance of preoperative

and postoperative studies. Of the remaining 23 patients who were treated preoperatively with beta adrenoceptor antagonists and vasodilators, only three patients were treated with beta receptor antagonists after operation and one patient was investigated while he was on nitrates only. Digoxin was not given to patients during the investigation period. Postoperative investigations were performed within three months of the operation.

EXERCISE TESTING

Before and after operation 41 of the 46 patients were exercised on a treadmill according to the modified Bruce protocol until they reached a symptom limited maximal level. Five patients who had unstable angina, frequent rest pain, and reversible electrocardiographic changes during pain were not exercised preoperatively.

AMBULATORY ST SEGMENT MONITORING

Before and after operation 48 hour ambulatory ST segment monitoring was performed in 34 patients and 24 hour monitoring was performed in 12 patients on a frequency modulated recorder (Oxford Medilog II) which accurately measures low frequency ($0.05 \text{ Hz} < 3 \text{ db down}$) signals.¹³ Two bipolar precordial leads, CM5 and a second lead resembling lead II, were recorded and the magnetic tapes were played back at 60 times normal speed. The number, duration, and magnitude of ST segment changes and the heart rate at the onset of ST segment changes were noted. Important ST segment depression was defined as depression $\geq 1 \text{ mm}$ occurring 0.08 seconds after the QRS complex and persisting for at least 30 s. ST segment elevation was defined as elevation $\geq 1 \text{ mm}$ at the J point.

Table 1 Characteristics (mean (SD)) of 46 patients studied; 32 (group 1) with daytime and 14 (group 2) with daytime and nocturnal ST segment changes during ambulatory monitoring

Characteristic	Group 1	Group 2
Number of patients	32	14
Age (years)	56 (8)	60 (9)
Duration of angina	> 1 year (n=28)*	> 1 year (n=12)†
Exertional pain	29	14
Rest pain	17	9
Previous myocardial infarction	10	7
Positive preoperative exercise test	28 (n=29)	12 (n=12)
Coronary angiogram:		
1 vessel disease	1	0
2 vessel disease	10	1
3 vessel disease	21	13
Left main stem stenosis	8	4

*Four patients had had angina for 3 months to 1 year.

†Two patients had had angina for 3 months to 1 year

CORONARY ARTERIOGRAPHY

Contrast left ventriculography and coronary cine angiography were performed in all patients before operation and in 34 patients after operation at the same time as aortography and catheterisation of grafts. Twelve patients refused the postoperative investigation because they were symptom free. Proximal stenosis of $\geq 70\%$ in a coronary artery was considered to indicate significant disease and left main stem stenosis was regarded as two vessel disease.

STATISTICS

Results are expressed as mean and standard deviation. Discrete data were analysed by the Wilcoxon signed rank test for paired observations and the χ^2 test.

Results

Table 1 summarises the preoperative characteristics of the 32 patients with daytime (group 1) and 14 patients with daytime and nocturnal (group 2) ambulatory ST segment changes who had undergone coronary bypass surgery. There were no significant differences between the ages of patients, the duration of angina, or the historical frequency of exertional and rest angina in the two groups, although 50% of group 2 patients had a history of previous myocardial infarction compared with 31% of group 1 patients (Table 1). All patients in group 2 had three vessel disease or left main stem stenosis, whereas a third of the patients in group 1 had one or two vessel disease. Preoperative exercise testing demonstrated a lower exercise threshold for ST segment depression in group 2 than in group 1 (Table 2). Group 2 patients also had more frequent episodes of long lasting ST segment change which were of greater magnitude and occurred at a lower heart rate than in group 1 patients (Table 3). These differences were, however, not shown to be statistically significant in these small groups of patients.

One to five (mean 3.4 (0.8)) bypass grafts were implanted. Postoperative cardiac catheterisation was performed in 24 group 1 patients (75%) and 10 group 2 patients (71%). Nine group 1 patients and four group 2 patients had all grafts patent with good distal run off. The overall graft patency rate (83%) was similar in both groups. Only 70% of the grafts were patent with good distal run off.

Recurrence of angina in the three month postoperative period (mean 22%) was similar in both groups ($p > 0.05$). Fifteen patients had positive postoperative exercise tests—seven (22%) in group 1 and eight (57%) in group 2 ($p < 0.01$) (Table 4). In these 15 patients, postoperative exercise duration

Table 2 Haemodynamic variables (mean (SD)) during preoperative treadmill exercise testing in 40 patients with a positive exercise test

Variable	Group 1	Group 2
	(Daytime ST changes)	(Daytime and nocturnal ST changes)
Number of patients	28	12
Resting heart rate (beats per minute)	71 (14)	67 (5)
Heart rate at 1 mm ST depression (beats per minute)	103 (19)	96 (10)
Duration of exercise to 1 mm ST depression (min)	5.1 (1.9)	3.5 (1.4)
No with chest pain during exercise	28 (100%)	11 (92%)

Table 3 Number, duration, and magnitude (mean (SD)) of painful and painless episodes of ST segment change during each 24 hour period of preoperative ambulatory monitoring in groups 1 and 2

	Group 1	Group 2
	(Daytime ST changes)	(Daytime and nocturnal ST changes)
Total number of episodes of ST segment change	1.7 (1.1)	11.4 (10)
Nocturnal episodes	0	2 (1.8)
Heart rate at onset of ST change (beats per min)	92 (17)	85 (12)
Duration of episodes (min)	25 (34)	38 (20)
Maximum magnitude of ST segment change (mm)	1.6 (1)	3.5 (1.3)
Number of painful episodes	0.9 (0.8)	3.1 (5.3)

Table 4 Comparison of preoperative and postoperative haemodynamic data (mean (SD)) obtained during exercise testing in 15 patients with positive exercise tests after operation

	Group 1		Group 2	
	Pre	Post	Pre	Post
Number of patients	7 (22%)		8** (57%)	
Resting heart rate (beats per min)	75 (12)	87 (16)	66 (6)	87 (17)*
Heart rate at 1 mm ST depression (beats per min)	107 (19)	137 (14)**	97 (12)	127 (14)**
Duration of exercise (min)	4.9 (2.1)	6.2 (3)**	3.0 (1)	6.4 (1.8)**
Patients with chest pain	7	3	7	4

* $p < 0.05$; ** $p < 0.01$.

and peak heart rate at which 1 mm segment depression occurred were both significantly higher than during the preoperative period ($p < 0.01$). This difference was more striking in group 2 patients, who had a proportionately greater improvement in postoperative exercise tolerance (Table 4). Only seven patients (three group 1 and four group 2) had pain associated with important ST segment depression at peak exercise postoperatively, whereas 14 of these 15 patients had experienced pain before operation. Eight patients were not on antianginal treatment during assessment before and after operation. Five patients who were on treatment preoperatively were assessed on no medication postoperatively and the remaining two patients were on the same medication before and after operation.

In sixteen patients, nine (28%) in group 1 and seven (50%) in group 2 ($p < 0.01$) ambulatory ST segment changes persisted after operation (Table 5).

In all these patients the number and the maximum magnitude of the episodes of ST segment change were significantly lower after operation ($p < 0.01$) (Table 5). This improvement was more striking in group 2 patients in whom the frequency of episodes was reduced by 62% than in group 1 patients in whom the frequency was reduced by 31%. Only two patients had nocturnal ST segment changes postoperatively, but these too were less frequent than during the preoperative period.

Thirty four patients were catheterised postoperatively; ambulatory ST segment changes recurred in 12 of them. Graft patency rates were not significantly different in patients with (81%) and those without (86%) postoperative ambulatory ST segment changes ($p > 0.05$). Eight of the 12 patients with recurrence of ambulatory ST segment changes after operation had total occlusion or narrowing of one or more grafts. Three of the remaining four

Table 5 Frequency, duration, and magnitude of painless and painful ambulatory ST segment changes before and after operation in 16 patients with recurrence of ST segment changes after operation

	Group 1		Group 2	
	Pre	Post	Pre	Post
Number of patients with ST changes after operation		9 (28%)		7** (50%)
Total number of episodes	4.9 (3)	3.4 (2.9)*	11.8 (9)	4.5 (3.3)**
Nocturnal episodes	0	0	2.1 (1.8)	0.4 (0.6)**
Heart rate at onset (beats per minute)	97 (11)	107 (12)**	85 (13)	98 (11)**
Duration (min)	23 (31)	27 (21)	37 (47)	34 (32)
Maximum magnitude of ST depression (mm)	2.5 (1.8)	1.5 (0.5)*	3.4 (1.3)	1.5 (0.5)*
Number of painful episodes (per 24 h)	1.6 (1.3)	0.2 (0.4)**	1.5 (1.6)	0.7 (0.5)**

* $p < 0.05$, ** $p < 0.01$.

patients had obstructive disease in ungrafted coronary arteries.

Discussion

After revascularisation 78% of patients had complete symptomatic relief of angina pectoris, and the frequency and severity of pain improved substantially in the remaining 22%. Treadmill exercise testing and ambulatory ST segment monitoring showed objective evidence of persistent postoperative myocardial ischaemia in 37% of the patients; two thirds of these were symptom free. Several studies have highlighted the frequency of ambulatory ST segment changes in patients with ischaemic heart disease,^{14,15} and haemodynamic and functional measurements have shown that both painful and pain-free episodes of ST segment change reflect myocardial ischaemia.^{16,17} In this study, some patients were free of postoperative angina but continued to show ST segment changes indicating silent ischaemia during normal daily activities.

Before operation patients with both daytime and nocturnal ischaemia had more severe coronary artery disease, a lower coronary reserve during exercise testing, and more frequent episodes of ambulatory ST segment changes which were of longer duration and greater magnitude. Operation in these patients produced complete revascularisation in 43%, and in the remaining 57% the severity of postoperative ischaemia was greatly improved. Nocturnal resting ischaemia was abolished in all but two patients and in these the frequency was significantly reduced. Indeed, postoperatively there was no significant difference between the frequency, magnitude, and duration of ambulatory ST segment changes or the exercise tolerance between group 1 and group 2 patients. Thus after revascularisation, patients with frequent nocturnal angina may also expect an improvement in their ischaemic threshold

with either complete relief of pain or with mainly effort related ischaemia only.

This study also demonstrates that freedom from angina postoperatively does not indicate absence of myocardial ischaemia, and even in patients who had recurrence of postoperative pain, angina frequency was a gross underestimate of the frequency of myocardial ischaemia as determined by ambulatory ST segment changes. The relative absence of pain postoperatively has been ascribed in previous studies to various factors such as interruption of afferent pain fibres, partial revascularisation, persistent collaterals, and psychological factors.¹⁸ Ambulatory ST segment monitoring accurately determines the presence, frequency, and magnitude of myocardial ischaemia.

There was no significant difference in graft patency between patients in whom there was postoperative myocardial ischaemia either during ambulatory monitoring or exercise testing, and those in whom there were no objective signs of inducible myocardial ischaemia after operation. Although some studies have shown a close correlation between graft patency, postoperative symptoms, and exercise tests,^{17,19,20} others,¹⁸ as in this study, have emphasised the poor relation between these features. Some patients with postoperative ambulatory or exercise induced ST segment changes were shown to have all grafts patent. Most of these patients, however, had obstructive disease distally in grafted vessels or in other ungrafted vessels. Also, there were some patients with an occluded graft or a graft with poor distal flow where ST segment changes could be detected postoperatively. Thus, as well as graft patency, the extent and severity of coronary artery disease in small or ungrafted vessels and the state of the collateral circulation may also be important factors in determining the recurrence of postoperative myocardial ischaemia and ST segment changes during ambulatory monitoring and exercise testing.

This study demonstrates the importance of obtaining objective evidence of complete revascularisation after coronary artery bypass graft surgery. Ambulatory ST segment monitoring provided an index of the frequency and magnitude of recurring myocardial ischaemia during normal daily activities, even though most episodes were free of pain. The prognostic implications of the occurrence of postoperative myocardial ischaemia need to be evaluated by long term follow up of this group of patients.

We thank the British Heart Foundation for their support.

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Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise

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SUMMARY Doppler echocardiography was used to measure stroke volume, peak flow velocity, and acceleration of flow in the ascending aorta in 10 healthy young volunteers during unlimited supine bicycle exercise and upright treadmill exercise. High quality studies were obtained in all subjects through the suprasternal notch acoustic window; there was no appreciable degradation in Doppler signal caused by interference by increased respiration or chest wall motion. Stroke volume index increased from 54 ml/m² at rest to 63.5 ml/m² at peak supine exercise and from 38 ml/m² standing at rest to 63.3 ml/m² during peak upright exercise. Mean peak flow velocity rose from 0.91 m/s at supine rest to 1.36 m/s during maximum supine exercise. In the upright position mean peak flow velocity increased from 0.75 m/s at rest to 1.39 m/s during maximum exercise. Mean peak velocities were lower in the upright position at rest but were not significantly different at peak exercise. Mean acceleration of flow in the ascending aorta increased from 12.02 m/s² during supine rest to 21.6 m/s² during supine exercise and from 10.8 m/s² at rest on the treadmill to 21.9 m/s² during peak upright exercise.

This study shows that echocardiographic measurement of ascending aortic blood flow by the Doppler technique is feasible even during vigorous exercise; that stroke volume and peak flow velocity at rest are lower in the upright position than in the supine position but equalise at peak exercise; and that acceleration of flow in the ascending aorta is the same in both the supine and upright positions and increases equally at peak exercise in both positions.

The relative contributions of increments in stroke volume and heart rate to the increase in cardiac output which accompanies exercise have been extensively studied with variable and sometimes contradictory results.¹⁻³ No change in stroke volume with exercise was found in early studies which used sonocardiometry to monitor left ventricular dimensions during exercise.¹ Subsequently, several studies used dye dilution⁴⁻⁶ or Fick methods⁷⁻⁹ to determine cardiac output and they showed an increase in stroke volume with exercise. Whereas invasive and non-invasive studies of the haemodynamic response to exercise have been performed, measurements made during maximal supine

bicycle exercise and maximal upright treadmill exercise in the same subjects have not been compared because of the technical limitations of available methods. Doppler echocardiography is suitable for such measurements and can be used to measure the velocity of blood flow in the ascending aorta during left ventricular ejection. Peak ascending aortic blood flow and acceleration of flow have been correlated with the maximum rate of rise of left ventricular pressure (dP/dt) and hence left ventricular function.¹⁰⁻¹³ Thus, changes in these variables with exercise may be useful for the non-invasive detection of exercise induced left ventricular dysfunction. Normal values of peak velocity and acceleration of blood flow in the ascending aorta during exercise are not known.

We have investigated the feasibility of performing Doppler echocardiography during exercise to measure the effects of unlimited exercise on stroke vol-

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Accepted for publication 22 July 1985

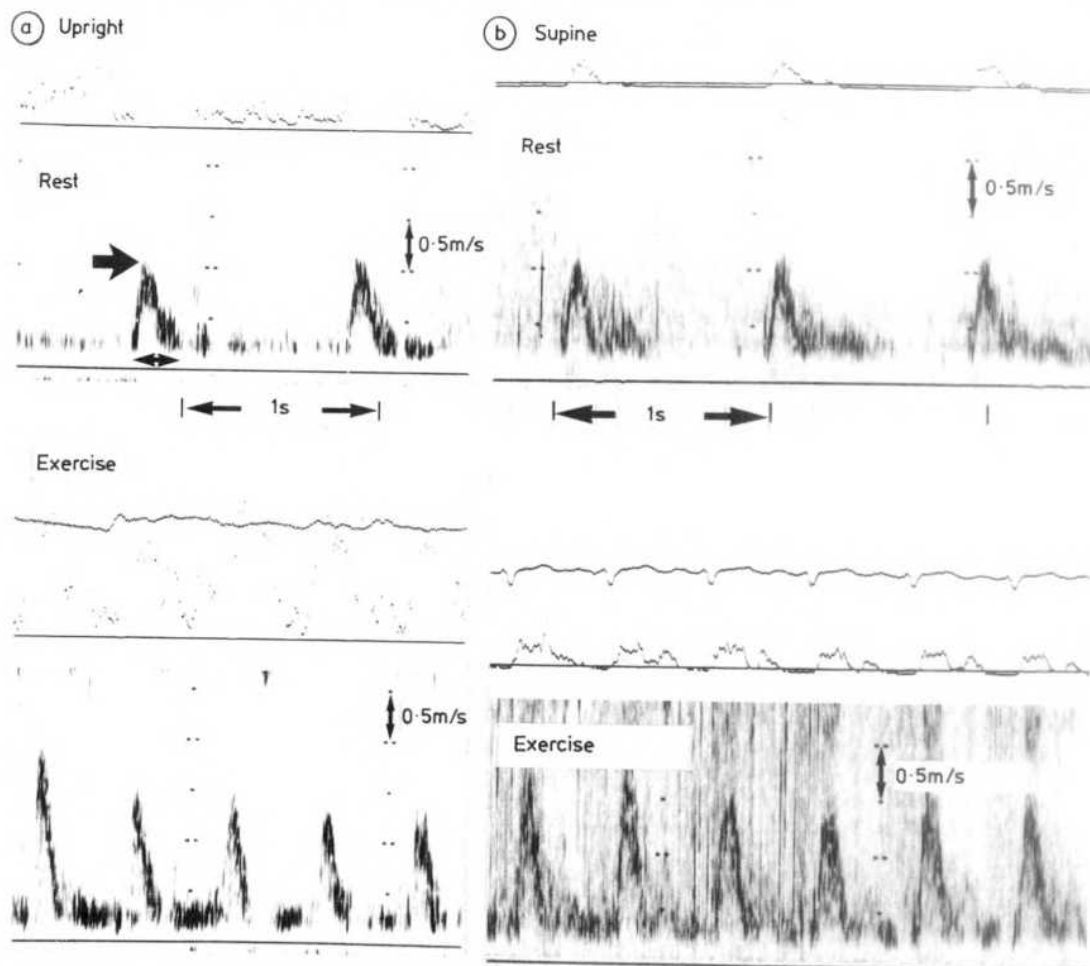


Fig. 1 Continuous wave Doppler echocardiographic recordings from the suprasternal notch at rest and during exercise in the upright (a) and supine (b) positions. Near the first beat during upright rest in (a) peak flow velocity is indicated by a large arrow and ejection time by a smaller double arrow.

ume during supine bicycle exercise and upright treadmill exercise and to obtain normal values for rest and exercise aortic blood flow peak velocities and acceleration.

Subjects and methods

We studied 10 healthy adults (six men and four women) mean age 27 years (range 25–31 years). None had important cardiac disease. All gave informed consent to a protocol approved by the human studies committee of the Medical College of Wisconsin.

Supine exercise was performed on a bicycle ergometer (Quinton) and was continued until exhaus-

tion. The upper body was kept flat with the legs raised to approximately 30° . Haemodynamic data were obtained at rest with the feet raised and strapped in place on the bicycle ergometer. Exercise was initiated at 200 kpm/min and was increased every 3 minutes by 100 kpm/min (women) or 200 kpm/min (men) ($1 \text{ kpm/min} = 0.167 \text{ W}$). Upright exercise was performed on an automated treadmill (Marquette CASE) following the Bruce protocol. Subjects exercised until exhaustion. During both supine and upright exercise, heart rate (electrocardiogram) and blood pressure were measured, and Doppler echocardiography was performed at each 3 minute workload. The rate-pressure product (heart rate $\times$ systolic blood pressure) was calculated at rest

and at peak exercise. Supine and upright studies were performed on different days so that the physical effects from the initial study did not influence subsequent exercise performance. The subjects were encouraged to exercise for as long as possible, but not all of them achieved true maximal exertion.

Doppler echocardiography was performed from the suprasternal notch with a 2 MHz dedicated Doppler transducer (Irex Medical Systems). To detect flow in the ascending aorta the transducer was angled anteriorly and to the right. Both graphic display and audio signals were used to find peak velocity envelopes with distinct borders (Fig. 1). Pulsed Doppler echocardiographic recordings obtained 7 to 10 cm from the suprasternal notch were compared with continuous wave Doppler recordings to confirm that the latter measured flow in the ascending aorta. When peak velocities exceeded the Nyquist limit of pulsed Doppler echocardiography during exercise only the continuous wave Doppler was used.

Cardiac output was calculated from Doppler echocardiography using the following formula¹⁴: $CO \text{ (ml/min)} = SVI \text{ (cm)} \times A \text{ (cm}^2\text{)} \times HR \text{ (beats/min)}$; where CO is cardiac output; SVI is systolic velocity integral, A is the cross sectional area of the aorta, and HR is heart rate.

The systolic velocity integral was determined by integrating the peak velocity curves (from systolic flow in the ascending aorta) over time. Peak velocity curves were integrated by computer (Franklin Insight 2000) by digitising hardcopy data (Fig. 1). Preliminary studies of 12 recordings obtained in three subjects at rest and during both supine and upright exercise revealed inter- and intraobserver variability of less than 9%, no more than 0.1 m/s in any recording. Data for this study were obtained by one observer who was unaware of the other findings or the state of exercise. The cross sectional area of the aorta was determined by measuring the diameter of the aortic root at the annulus with M mode echocardiography guided by cross sectional echocardiography (Irex Medical Systems).¹⁴ The largest aortic diameter in systole and the diameter at end diastole were averaged.¹⁵ The area (A) of the aorta at the annulus was calculated as: $A = \pi (\text{diameter}/2)^2$. Cardiac indices were determined by multiplying stroke volume indices and heart rate.

Acceleration of flow in the ascending aorta was determined from hardcopy data and the formula: $\text{acceleration} = V_{\text{peak}}/TP$. Time to peak velocity (TP) was calculated from the time of onset of flow to the time at which velocity of flow was maximal (V_{peak}) (Fig. 1).

Each of the study variables was analysed with a two way analysis of variance (four conditions by 10

subjects) and the least significant difference test was then used to assess specific comparisons.¹⁶ The four conditions were: (a) supine rest, (b) supine exercise, (c) upright rest, and (d) upright exercise. The F test for analysis of variance was significant for 10 (for $(a)=(b)=(c)=(d)$). The least significant difference test was used to test $(a)=(b)$, $(a)=(c)$, $(b)=(d)$, and $(c)=(d)$. Data were summarised as mean and standard deviation. A probability level of ≤ 0.05 was taken to indicate statistical significance.

Results

Good quality Doppler echocardiograms were obtained at rest and through all levels of exercise without difficulty. The mean stroke volume index was 42% higher in the supine position at rest than in the standing position at rest ($p < 0.01$). At peak exercise the mean stroke volume index was not significantly different in the supine and upright positions (Fig. 2). Whereas the mean stroke volume index increased by 19% from rest to peak exercise in the supine position, the increase (66%) from rest to peak exercise in the upright position was far greater. Mean cardiac index was not significantly different at rest or peak exercise in the supine and upright positions. Although the mean resting heart rate was lower in the supine position than in the upright position, the difference was not statistically significant. At peak exercise the heart rate was lower in the supine position than in the upright position ($p < 0.05$) (Fig. 3).

The mean maximum heart rate at peak supine bicycle exercise was 138 beats/minute with individual values ranging from 112 beats/minute to 161 beats/minute. During peak upright treadmill exercise the mean maximum heart rate was 151 beats/minute with values ranging from 127 beats/minute to 191 beats/minute.

The mean double product increased with exercise but was not significantly different in the supine and upright positions (Fig. 3). Mean peak blood flow velocity in the ascending aorta was 0.91 m/s at supine rest with the feet elevated and increased to 1.36 m/s during peak supine exercise (Fig. 4). At rest in the upright position mean peak velocity was 0.75 m/s and increased to 1.39 m/s during maximum upright exercise. Mean peak velocity was significantly lower in the upright position at rest ($p < 0.05$) than in the supine position but not at peak exercise (Fig. 4). Mean acceleration of blood flow in the ascending aorta increased from 12.02 m/s² during supine rest to 21.16 m/s² during supine exercise ($p < 0.01$). In the standing position mean acceleration increased from 10.8 m/s² at rest to 21.9 m/s² during peak exercise ($p < 0.01$). Mean acceleration was not

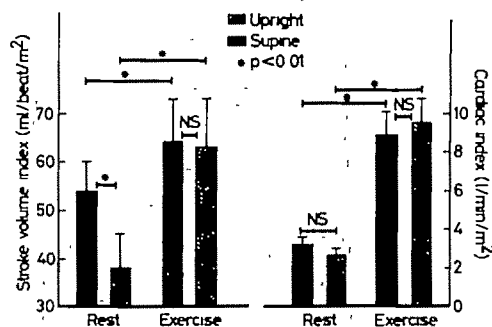


Fig. 2 Changes in mean (SD) stroke volume index and mean (SD) cardiac index during supine and upright exercise. Stroke volume index rose from 53.9 (6.3) ml/beat/m² in the supine position at rest to 63.5 (8.8) ml/beat/m² at exercise and from 38 (6.7) ml/beat/m² upright at rest to 63.3 (9.9) ml/beat/m² at exercise. Cardiac index rose from 3.2 (0.4) ml/min/m² supine at rest to 8.7 (1.5) ml/min/m² at exercise and from 2.6 (0.3) l/min/m² upright at rest to 9.5 (1.3) l/min/m² during upright exercise.

significantly different in the supine and upright positions (Fig. 4).

Discussion

The effects of exercise on cardiovascular function have intrigued investigators for decades. The response of the heart to increased demand is of fundamental physiological importance and plays a major role in the clinical detection and quantification of

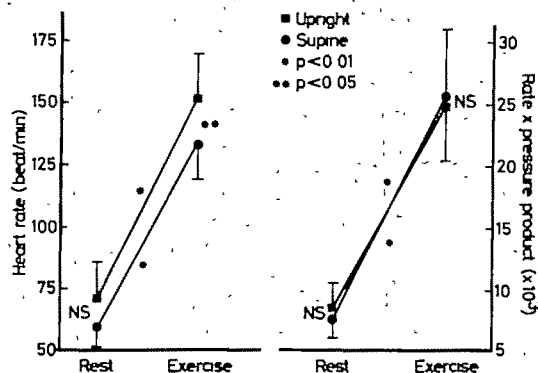


Fig. 3 Changes in mean (SD) heart rate and mean (SD) rate-pressure product during supine and upright exercise. Heart rate rose from 60 (9) beats/min at supine rest to 138 (16) beats/min at exercise and from 71 (15) beats/min at upright rest to 151 (21) beats/min during exercise. Rate pressure product rose from 7.8 (1.7) at supine rest to 25.5 (5.5) at exercise and from 8.7 (8) at upright rest to 25 (5) at exercise.

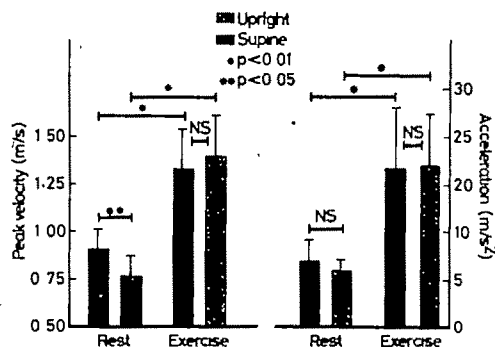


Fig. 4 Changes in mean (SD) peak flow velocity and mean (SD) acceleration of flow in the ascending aorta during exercise. Peak flow velocity during supine rest was 0.9 (0.1) m/s rising to 1.4 (0.2) m/s with exercise. Upright resting peak velocity was 0.8 (0.1) m/s rising to 1.4 (0.3) m/s with exercise.

heart disease. While many studies have been performed to evaluate the haemodynamic response to exercise in the supine and upright positions, accurate methods of measuring variables such as stroke volume, peak velocity of ascending aortic blood flow, and acceleration of flow during high levels of exercise in both the supine and upright positions have only recently become available. The accuracy of Doppler echocardiography in measuring stroke volume in subjects at rest has been clearly demonstrated.^{14,17-19} The technique has also been used during low-level exercise in patients with mitral stenosis²⁰ and in normal subjects.²¹

We have shown that Doppler echocardiography in which the suprasternal notch is used as an acoustic window can be performed in normal subjects during rigorous exercise. Respiratory interference during exercise was not a major problem because the ultrasound beam traversed the mediastinum to reach the ascending aorta and did not come into contact with the lung. In addition, lower frequency ultrasound has a better penetrating capacity and can be successfully used in Doppler echocardiography. The high signal to noise ratio of the dedicated continuous wave Doppler system we used was particularly useful in obtaining diagnostic quality data at peak exercise. While the success rate will probably be less when large numbers of patients rather than healthy subjects are studied with this technique, the ease with which we were able to record Doppler signals during exercise is encouraging.

We found an increase in stroke volume and peak velocity of flow in the ascending aorta with exercise.

Table Stroke volume index measured by Doppler echocardiography during supine and upright rest and exercise

	Stroke volume index (ml/m ²)				Method	
	Supine*		Upright		Cardiac output	Upright exercise
	Rest	Exercise	Rest	Exercise		
Wang <i>et al</i> (1960) ⁶	53	60	32	59	Dye	Treadmill
Frick and Somer (1964) ⁸	51	68	—	—	Fick	—
Bevegård <i>et al</i> (1966) ⁷	56	68	38	63	Fick	Bicycle
Poliner <i>et al</i> (1980) ²⁴	42	58	30	54	Radionuclide angiography	Bicycle
Medical College of Wisconsin	54	64	38	63	Doppler	Treadmill

*All supine exercise performed on bicycle.

At rest, stroke volume and peak velocity are greater in the supine than the upright position. Heart rate is slightly higher in the upright position to maintain cardiac output. During exercise in the supine position, stroke volume and peak velocity increase but not nearly to the degree that they increase in the upright position. During peak exercise, stroke volume and peak velocity are not significantly different in the supine and upright positions. Acceleration of flow in the ascending aorta increased with exercise but was not significantly different in the supine and upright positions, suggesting that this variable is independent of preload (Frank-Starling phenomenon).

The mechanism responsible for postural differences in the haemodynamic response to exercise is uncertain.^{1,27} Changes in stroke volume during exercise were not found in early studies,¹ but most subsequent data, like ours, showed an increase in stroke volume during exercise.^{7,15,22} Increased myocardial contractility contributes to the increase in stroke volume with exercise.^{2,23} The role of the Frank-Starling mechanism is controversial; however, recent data suggest that stroke volume during exercise is increased by a combination of the Frank-Starling mechanism and an enhanced contractile state.^{24–26} Changes in the preload of the left ventricle also contribute to changes in stroke volume. Venous return is augmented in the supine position and this contributes to the greater stroke volume achieved. Raising the legs and strapping feet into place on the bicycle ergometer increased stroke volume by 19% compared with stroke volume in the supine, legs flat position.⁸ The muscle pump action of the legs is important in augmenting venous return in the upright position. During upright exercise when only the arms are used stroke volume is lower throughout exercise and never rises as high as stroke volume during upright exercise with the legs.^{3,7} Finally, changes in systemic impedance are also of importance in causing changes in stroke volume.²⁷

Thus increases in stroke volume with exercise are brought about by various interacting mechanisms. Our data show that these mechanisms result in similar stroke volumes at peak exercise in the supine and upright positions whereas at rest stroke volume is lower in the upright position.

In the Table we compare our results with those obtained in other studies of normal volunteers of similar age that used invasive techniques and radionuclide ventriculography. Using the cardiogreen dye indicator dilution method during supine and upright exercise, Wang *et al*⁶ showed changes in cardiac output nearly identical to ours. Bevegård *et al*⁷ and Frick and Somer⁸ used the Fick principle to show changes in cardiac output with supine and upright exercise similar to those we demonstrated with Doppler echocardiography. Using radionuclide ventriculography, Poliner *et al* reported lower resting stroke volume indices than those found by others and they did not detect an increase in stroke volume with elevation of the legs in the supine position.²⁴ The fact that our measurements of stroke volume by Doppler echocardiography correlated closely with stroke volume determined invasively confirms the accuracy of the Doppler technique.

We also measured peak velocity and acceleration of flow in the ascending aorta at rest and during exercise. In previous invasive studies a correlation between ascending aortic blood flow velocity and left ventricular function was noted.^{10–12} Acceleration of flow has been related to dP/dt and thus is regarded as an index of left ventricular function^{10–13} Similarly, changes in peak flow velocity have been shown to reflect changes in left ventricular contraction induced by positive inotropic stimulation.¹⁰ After intravenous propranolol, depression in myocardial function can be detected by decreases in maximal blood flow velocity, acceleration, and dP/dt.¹² Our data for peak flow velocity and acceleration are similar to those obtained by electromagnetic velocity sensors.¹² Measurement of ascending aortic blood flow

velocity and acceleration by Doppler echocardiography provides a non-invasive means of assessing left ventricular function. Monitoring of these variables during exercise may allow detection of exercise induced left ventricular dysfunction.

Exercise Doppler echocardiography may have several limitations. We used an average of systolic and diastolic potential diameters to calculate cardiac output.^{14,28} Since we were unable to measure the aortic annulus diameter during exercise, we used the resting value to calculate stroke volume during exercise. This seems reasonable since aortic dimensions at the annulus do not change significantly when cardiac outputs are increased fourfold with dobutamine infusion.¹⁴ In an animal model too, it has been shown that aortic dimensions do not change significantly over a wide range of cardiac outputs.²⁹ Nevertheless, determination of aortic diameter is a well known source of error when Doppler echocardiography is used to measure stroke volume.

Limitations in Doppler instrumentation and technique may prevent accurate recording of peak velocity profiles, especially if only pulsed wave Doppler echocardiography is used. Care must be taken to locate the peak velocity profile when the interrogating beam is parallel to flow in the ascending aorta. There may be difficulties when this method is used in older patients with cardiac disease who may not have laminar flow in the ascending aorta.

We have demonstrated that stroke volume, peak velocity, and acceleration of ascending aortic blood flow can be measured by Doppler echocardiography during vigorous supine bicycle exercise and upright treadmill exercise. Different responses to supine and upright exercise were shown by the technique, which appears to have considerable potential for evaluation of patients with known or suspected heart disease.

We thank Dr John H Kalbfleisch for the statistical analysis.

This study was supported in part by the NIH/NHLBI, Bethesda, Maryland, the Veterans Administration, Washington, DC, and the American Heart Association, Milwaukee, Wisconsin, USA.

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Sinus node sequences after atrial stimulation: similarities of effects of different methods

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SUMMARY Sinoatrial conduction is commonly assessed from features of the initial cycle after a single atrial extrastimulus or eight beats atrial pacing. In contrast, sinus node automaticity is assessed by the duration of the first interval after prolonged atrial pacing. The return cycle and initial sequences after these different methods were compared in 10 subjects with normal sinus node function and 30 patients with sick sinus syndrome. Typically, sequences after all three methods showed a maximally prolonged first interval with a progressive decrease over five or more cycles. A model of recovery from overdrive suppression was used to compute the elements of conduction time and automaticity in the first interval. The sequences which followed a single extrastimulus and pacing were similar, the only index which increased significantly with prolonged pacing was associated with the degree of suppression of automaticity. The computed component of sinoatrial conduction in the return cycle was similar for all three methods. Thus all three conventional methods which consider only the initial post-stimulation interval measure both sinoatrial conduction and sinus node automaticity. The separate components of automaticity and conduction may be assessed by analysis of the total sequence.

Assessment of sinus node function is important in those patients presenting with symptoms suggestive of the sick sinus syndrome¹ in whom diagnostic electrocardiographic features are either absent or equivocal. Investigations which may provide valuable additional information include prolonged ambulatory electrocardiographic monitoring,^{2,3} assessment of the heart rate response to autonomic interventions such as exercise and drugs,^{4,5} and intracardiac electrophysiology study.

Two basic procedures are used in the electrophysiological assessment of sinus node function. In the first the response to prolonged overdrive right atrial pacing for periods of between 30 s and 5 min is assessed.⁵⁻⁹ The interval between the last pacing stimulus and the first spontaneous atrial electrogram, "the sinus node recovery time", has been widely used as a measure of sinus node automaticity. A variant of this index is the "corrected sinus node recovery time", which is the recovery time minus

the pre-pacing cycle length.⁹ A second group of tests is used to assess sinoatrial conduction time; these are usually based on the responses of the sinus node to a single atrial extrastimulus.¹⁰ The response of the sinus node to fixed rate pacing for eight beats at a cycle length just short enough to achieve atrial capture¹¹ or more recently direct electrode recording of prepotentials from the sinus node region are alternative approaches.¹²⁻¹⁴ In recent years electrophysiological study has fallen out of favour, partly because of the considerable overlap of conventional indices between subjects with clinically normal sinus node function and those with abnormal sinus node function.

A mathematical model of recovery of the sinus node after overdrive suppression has been developed.¹⁵ When this is applied to the sequences that follow one minute of overdrive atrial pacing, separate indices of sinoatrial conduction and sinus node automaticity can be derived. Preliminary observations have suggested that the sequences that follow single atrial extrastimuli qualitatively resemble those that follow fixed rate pacing.

We have applied this mathematical model to different pacing modalities to compare their effects on sinus node function. We hoped that this might

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Accepted for publication 22 July 1985

lead to the development of better methods for evaluation of sinus node function.

Patients and methods

PATIENT SELECTION

Thirty patients, aged 18–93 years (mean (SD) 71(14) years) were diagnosed as having the sick sinus syndrome on the basis of having symptoms of pre-syncope or syncope, and evidence of inappropriate sinus bradycardia, sinoatrial exit block, or sinus arrest. Many also had palpitation and evidence of atrial tachyarrhythmias, but these symptoms by themselves were regarded as not being sufficient for diagnosis of the syndrome.

Another 10 patients, aged 21–66 years (mean 37(15) years), had clinically normal sinus node function without a history of syncope or presyncope or bradyarrhythmias. These patients had electrophysiological study for investigation of regular, narrow QRS complex tachycardias.

ELECTROPHYSIOLOGICAL STUDY

Multiple 6 French electrode catheters were positioned under fluoroscopic control in fasting and non-sedated patients in whom cardioactive drugs has been discontinued for at least five elimination half-lives, and who had given their informed consent. A quadripolar electrode was positioned in the high right atrium for recording (proximal pair) and stimulating (distal pair), a tripolar electrode across the tricuspid valve to record the His bundle electrogram, and a bipolar electrode in the right ventricular apex for stimulation. Intravenous heparin 5000 units was given on completion of electrode placement. Programmed stimulation was performed with a Devices Neurolog isolated source stimulator. Surface electrocardiographic leads and three or four concurrent intracavitary electrograms were recorded at 100 mm/s chart speed on a Minograph Model 62 recorder.

After a ten minute rest period, cycle length was recorded for one minute. Programmed stimulation was then undertaken to obtain the following data:

(a) Responses after fixed rate stimulation for one minute. Responses were assessed after three to five trials of one minute of overdrive high right atrial pacing at 100 beats per minute and at 130 beats per minute. A two minute rest period was allowed between each pacing trial.

(b) Responses after fixed rate stimulation for eight beats. Pacing trials were repeated 10 times in each patient, sinoatrial conduction time being calculated as the increment in the immediate post-stimulation interval above the mean of 20 prepacing cycle lengths.

(c) Responses to single atrial premature stimuli. Stimuli with coupling interval A_1 were introduced after every eighth beat during sensed sinus rhythm. The first stimuli were placed at the end of diastole and the coupling interval was reduced by 10–20 ms until atrial refractoriness was detected. The sinus cycle lengths immediately preceding and following the premature stimulus were designated A_1 and A_2 respectively.

The sequences following atrial stimulation were digitised by means of a Hewlett Packard Model 9874A digitiser, 9872A plotter, and 9825A calculator with programs specifically written for this purpose. The first post-pacing interval was measured from the pacing spike to the initial rapid deflection of the first spontaneous high right atrial electrogram. For all the sequences that followed these different methods of stimulation we plotted cycle length against beat number. In addition, from the responses to single extrastimuli we plotted the normalised return cycle (A_2/A_1) against the normalised test cycle (A_1/A_1). Sinoatrial conduction time was estimated from this plot as described by Strauss¹⁰ as the mean value of A_1 in the last third of the zone of reset minus the mean value of A_1 .

MATHEMATICAL MODEL

The mathematical model we used was developed by Dr Arie Helfgott in this laboratory.¹⁵ In brief, if responses after overdrive suppression are the consequence of a single elimination or degradation process (such as clearance of extracellular potassium), and if constant action potential duration, constant difference between maximum diastolic and threshold potentials, capture and reset of the sinus node by all atrial extrastimuli, and absence of pacemaker shifts are assumed, recovery may be regarded as depending solely on the increase in the slope of phase 4 depolarisation.¹⁵ From this it can be shown that recovery and decrease in cycle length conforms to an exponential equation (Fig. 1):

$$T_j = T_\infty + (T_1 - T_\infty) \cdot q^{j-1}$$

In this relation, j is an arbitrary notation for any beat in the sequence, T_j its cycle length, T_∞ the asymptotic cycle length to which recovery tends, and q is simply a measure of the rate of recovery (the common ratio) during the sequence.

COMPUTATIONS

Sequences were regarded as being suitable for fitting to the model if the following criteria were satisfied: (a) progressive decrease in post-pacing cycle length until at least the fifth interval, suggesting at least a degree of suppression of automaticity by atrial stimulation; (b) there were no ectopic or escape beats in

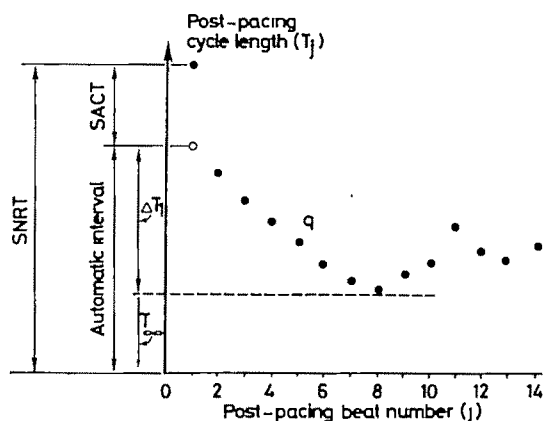


Fig. 1 Schema illustrating sinus node recovery after atrial stimulation. Post-pacing cycle length is plotted against post-pacing beat number. Closed circles represent measured intervals and open circle the first interval extrapolated from the curve of best fit to the rest of the sequence. The first interval, the conventional sinus node recovery (SNRT) has components relating to composite sinoatrial conduction time (SACT) and an automatic sinus node interval with an increment (ΔT_1) due to suppression of automaticity by atrial stimulation. As the sinus node recovers the subsequent sequence takes the form of an exponential (decaying geometric progression with common ratio, q) tending towards an asymptotic cycle length (T_∞). Reproduced with permission from PACE, 1984;7:735-48.

the sequence; (c) no change in P wave morphology or atrial activation sequence to suggest pacemaker shift to a focus other than the sinus node.

Atrial electrograms do not directly measure sinus node activity. In particular, after atrial stimulation which captures the sinus node, the first interval must contain two components; an automatic interval and an additional component of sinoatrial conduction into and out of the sinus node from the electrode (Fig. 2). If anterograde (sinoatrial) conduction time is regarded as being constant, then electrograms after the first cycle accurately measure the recovery of automaticity. Accordingly, we used a computer program based on non-linear least squares techniques to obtain the curve of best fit to the second and subsequent cycles of all "acceptable" sequences, and from these we extrapolated a theoretical first automatic cycle. Computed sinoatrial conduction time was then derived as the difference between the measured first post-pacing cycle length and this extrapolated theoretical first cycle length (see Results). In the relation described, potential indices of sinus node automaticity are q , T_∞ , and the increment in the first interval (T_1) due to suppression of automaticity ($\Delta T_1 = T_1 - T_\infty$).

For successful fitting of sequences to the model

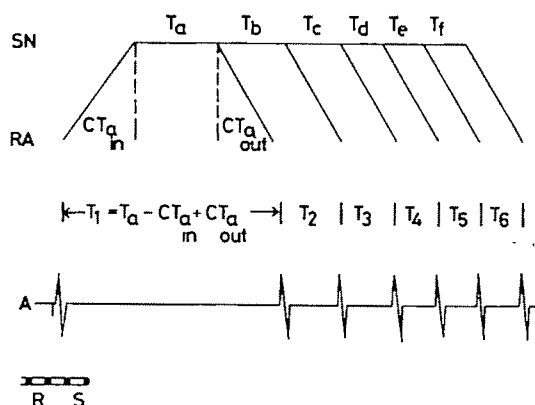


Fig. 2 Ladder diagram representing the sinus node (SN) and high right atrium (RA), and recording of high right atrial electrograms (A). R and S are the recording and stimulating pairs of the atrial electrode catheter. After the last atrial extrastimulus which captures the SN (either with fixed rate pacing or a single extrastimulus), retrograde conduction (CTa_{in}), the SN automatic interval (Ta), and anterograde conduction time (CTa_{out}) make up the first interval (T_1) as recorded in the RA. If subsequent sinoatrial conduction times are constant, the measured intervals T_2 , T_3 , etc., reflect subsequent SN automatic intervals Tb , Tc , etc. Reproduced with permission from PACE, 1984;7:735-48.

the following were regarded as necessary: (a) ΔT_1 , computed sinoatrial conduction time and $T_\infty > 0$; (b) $1 > q > 0$; (c) residual mean square < 1000 . The multiple correlation coefficient R^2 was used as a measure of goodness of fit and was usually > 0.98 .

STATISTICAL ANALYSIS

Data are presented as means (1 SD). Indices in each group after single extrastimuli were compared with indices after atrial pacing by means of Student's paired t test. A given index in the two patient groups was compared by means of an unpaired Student's t test. A p value < 0.05 was regarded as significant.

Results

CLINICAL INDICES

Tables 1 and 2 show basic electrophysiological data in the groups with normal and abnormal sinus node function respectively. Both mean age and resting cycle length were significantly greater in those with the sick sinus syndrome ($p < 0.0001$ for both).

SINOATRIAL CONDUCTION TIME CALCULATED FROM ATRIAL EXTRASTIMULI

In nine of 10 patients with normal sinus node function and in 23 of 30 patients with the sick sinus syn-

Table 1 Basic electrophysiological data in 10 patients with normal sinus node function

Case No	CL (ms)	T ₁ Strauss (reset) (ms)	T ₁ Narula (ms)	SNRT 100 bpm (ms)	SNRT 130 bpm (ms)	SACT APB (ms)	SACT		SACT computed after		
							8 beats pacing (ms)	APB (ms)	8 beats pacing (ms)	FRP 100 bpm (ms)	FRP 130 bpm (ms)
1	865	1108	1160	1242	1216	173	225	116	69	45	18
2	815	1103	1093	1177	1210	168	145	nc	84	61	46
3	430	629	625	—	626	124	94	nc	52	—	59
4	820	883	1121	1154	1114	206	371	127	216	211	nc
5	850	1090	1114	1189	1098	166	189	84	64	53	82
6	690	868	873	921	886	124	175	nc	88	140	119
7	580	696	—	—	654	93	—	84	—	—	92
8	900	1069	—	1185	1124	nc	—	89	—	10	nc
9	830	1003	989	1047	979	160	194	108	115	144	149
10	745	944	947	869	956	281	237	111	91	68	208
Mean	753	939	990	1085	986	166	204	103	97	92	96
(1 SD)	148	171	178	126	211	55	81	17	52	67	61

CL, resting cycle length; T₁ Strauss and T₁ Narula, mean first interval after single atrial extrastimulus or eight beats atrial pacing during Strauss and Narula conduction time determinations; SNRT, sinus node recovery time; SACT APB, sinoatrial conduction time after single extrastimuli, FRP, fixed rate pacing, SACT 8 beats pacing, sinoatrial conduction time after eight paced beats, —, not done; nc, unable to derive or compute sinoatrial conduction time after single extrastimulus from post-stimulation sequence by application of the model.

Table 2 Basic electrophysiological data in 30 patients with sick sinus syndrome

Case No	CL (ms)	T ₁ Strauss (reset) (ms)	T ₁ Narula (ms)	SNRT 100 bpm (ms)	SNRT 130 bpm (ms)	SACT APB (ms)	SACT		SACT computed after		
							8 beats pacing (ms)	APB (ms)	8 beats pacing (ms)	FRP 100 bpm (ms)	FRP 130 bpm (ms)
1	740	1120	860	1390	1250	141	116	115	nc	353	132
2	1040	1307	1323	1267	1052	212	285	147	143	nc	206
3	870	1198	1136	1287	1319	288	286	157	182	96	189
4	905	1084	1080	1288	1615	188	199	217	142	261	523
5	975	1133	1092	1246	1196	212	184	nc	163	244	237
6	1130	1197	—	3699	4345	52	—	nc	—	nc	nc
7	1210	1338	1675	2045	1777	nc	497	269	324	nc	nc
8	1115	1256	1268	1426	1425	130	113	69	110	138	123
9	1090	1236	1323	1227	957	162	114	98	91	nc	159
10	1020	1243	1241	1340	1301	230	211	189	154	296	89
11	730	1015	946	1767	2884	212	224	237	204	nc	nc
12	1140	1324	1346	1087	1079	131	148	61	106	132	23
13	1450	1631	1626	1543	1491	72	84	nc	27	nc	nc
14	1000	1228	1238	1357	1585	192	220	nc	164	258	275
15	1165	1405	1492	1279	1032	198	247	nc	81	137	nc
16	1130	1333	1322	1542	1935	156	157	104	105	205	97
17	1090	1193	1131	924	885	181	194	223	188	35	nc
18	1300	nc	—	1475	1594	nc	—	—	—	nc	nc
19	750	1014	—	1348	1568	nc	—	nc	—	442	nc
20	910	1343	—	1403	1344	nc	—	141	—	222	nc
21	730	886	—	973	1093	157	—	103	—	131	178
22	800	921	—	1082	923	nc	—	nc	—	190	81
23	1155	1066	—	1156	1152	291	—	111	—	94	135
24	1225	1556	1497	1239	—	285	388	271	245	nc	—
25	825	1272	1320	1288	1301	209	240	126	143	143	330
26	1020	1350	1421	939	2373	313	406	253	302	16	nc
27	1040	840	1139	1121	1181	nc	304	nc	nc	58	197
28	1015	1182	1172	1280	1149	155	159	131	127	81	49
29	935	1253	1277	1387	1455	309	270	nc	176	358	no
30	1165	nc	—	2036	2231	nc	—	—	—	nc	nc
Mean	1022	1212	1269	1415	1541	195	229	159	159	185	178
(1 SD)	179	182	200	506	707	70	103	67	71	114	119

See footnote to Table 1 for abbreviations

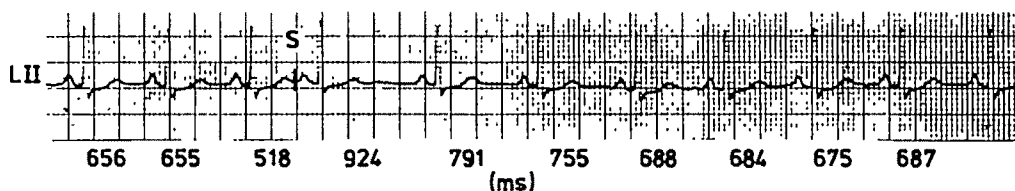


Fig. 3 Electrocardiographic lead (L)II showing prolongation of not only the first but also subsequent cycle lengths (in ms) after a single atrial extrastimulus (S). (Measurements made from intracardiac recordings).

drome, sinoatrial conduction time after single extrastimuli could be derived from the plot of A_r/A_1 against A_1/A_1 (Tables 1 and 2). In those in whom it could not be calculated, either the points were widely scattered or, in the patients with sick sinus syndrome, there was no reset zone (3/7) or probable sinoatrial exit block (2/7). Sinoatrial conduction time in the patients with normal sinus node function (166 (55)ms) was not significantly different from that in the patients with sick sinus syndrome (195 (70)ms).

SINOATRIAL CONDUCTION TIME AFTER FIXED RATE ATRIAL PACING (EIGHT BEATS)

In eight patients with normal sinus node function and in 22 patients with the sick sinus syndrome, sinoatrial conduction time was assessed by the method described by Narula *et al.*¹¹ and mean values were 204(81)ms and 229(103)ms, respectively (difference not significant).

SINUS NODE RECOVERY TIME

After atrial pacing at 100 beats per minute, mean sinus recovery time was significantly greater ($p < 0.0001$) in the patients with sick sinus syndrome (1415 (506)ms) than in those with normal sinus node function (1085 (126)ms). The sinus node recovery time at 100 beats per minute could not be obtained in two patients with normal sinus node function whose resting cycle length was less than 600ms. Similar differences between those with normal and abnormal sinus node function were found after pacing at 130 beats per minute.

GROSS ANALYSIS OF SEQUENCES AFTER ATRIAL STIMULATION

Figure 3 shows an electrocardiographic recording of the typical events after an atrial extrastimulus in the zone of reset. Figure 4 illustrates this result as a plot of cycle length against beat number. After the return cycle there was a progressive decrease in cycle length, indicating suppression and then progressive recovery of automaticity.

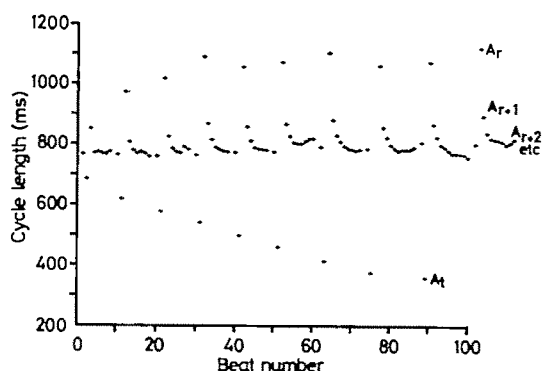


Fig. 4 Plot of cycle length against beat number during estimation of sinoatrial conduction time by single atrial extrastimulus (A_r). For purposes of illustration, responses to many extrastimuli are excluded; all followed the same pattern. The extrastimuli are shown in the lower half of the figure. After these extrastimuli, sequences had a maximally prolonged first interval in the return cycle (A_r) and then a progressive decrease in subsequent cycles (A_{r+1} , A_{r+2} , etc). Reproduced with permission from PACE, 1984;7:735-48.

Cycle length decreased until after the fourth post-stimulation interval in seven of the 10 patients with normal sinus node function and 19 of the 30 with abnormal sinus node function, when test extrastimuli were introduced during the zone of reset. This decrease often continued until the next extrastimulus was given eight cycles later.

In all eight patients with normal sinus node function and in 20 of 22 with abnormal sinus node function, sequences after atrial pacing for eight beats had the same form—that is with maximally prolonged first post-pacing interval and a decrease in subsequent cycles. Sinoatrial exit block and widely scattered cycle lengths made sequences in the other two patients with sick sinus syndrome unsuitable for detailed analysis by the model. Sequences of post-pacing intervals were similar in most of the trials after one minute of atrial pacing. Cycle length tended to decline, irrespective of the pacing mode (after

pacing at 100 beats per minute in 27/30 trials in the patients with normal sinus node function and in 56/95 trials in the patients with sick sinus syndrome). Thus, the mathematical model could be used to compare the effects of the different methods.

COMPUTED INDICES AND ANALYSIS OF SEQUENCES

After single extrastimuli

Thirty nine of the 45 sequences suitable for computation in those with normal sinus node function and 170 of 208 in patients with sick sinus syndrome were successfully fitted. With the exception of one patient with normal sinus node function and one with sick sinus syndrome, all 25 patients in whom indices could be computed were from the 32 in whom sinoatrial conduction time could be derived as described by Strauss *et al.*¹⁰ In the other patients, scatter of cycle lengths, sinoatrial exit block, or frequent spontaneous extrasystoles prevented the derivation of either the conventional or the computed sinoatrial conduction time. When the Strauss conduction time could be derived but the sequences were unsuitable for computation, the post-pacing sequences did not show decay of cycle length for more than four intervals.

A comparison of results in the six patients with normal sinus node function and in the 17 with the sick sinus syndrome in whom sinoatrial conduction time after single extrastimuli could be derived conventionally and computed from the model showed that the computed sinoatrial conduction time was significantly less than the conventional sinoatrial conduction time in both patient groups ($p < 0.025$ for both). This is of course to be expected because computed sinoatrial conduction time is simply conventional sinoatrial conduction time minus an element ΔT_1 that we attribute to depression of sinus node automaticity. Of considerable importance, however, is the improved ability of computed sinoatrial conduction time to differentiate between patients with a sick sinus and those without. Mean computed sinoatrial conduction time in the controls was 103 ms with a standard deviation of 17 ms, giving a "range" (mean (2 SD)) of 69–137 ms. Nine of the 18 patients with sick sinus syndrome (50%) fell outside this range. Mean sinoatrial conduction time derived by the method of Strauss was 166 ms with a standard deviation of 55 ms, giving a "normal" range of 56–276 ms, which includes all but four of the sick sinus group.

Of the indices of automaticity after an atrial premature beat, T_∞ was significantly greater in those with sick sinus syndrome ($p < 0.025$), while q and ΔT_1 were not significantly different from values in patients with normal sinus node function.

After eight beats fixed rate pacing

Computed indices in both groups of patients strongly resembled indices derived after single extrastimuli and overdrive pacing for one minute. The mean values of ΔT_1 were intermediate between those after single atrial extrastimuli and atrial pacing at 100 beats per minute and were not significantly different (178 (51) ms in controls and 172 (112) ms in those with sick sinus syndrome) in the two patient groups.

As was found after a single extrastimulus, computed sinoatrial conduction times (97 (52) ms in controls and 159 (71) ms in the sick sinus syndrome) were significantly different ($p < 0.025$) in the two patient groups. T_∞ was significantly longer in the group with sick sinus syndrome (1003 (187) ms) than in the controls (721 (111) ms, $p < 0.0005$).

After one minute of fixed rate pacing

The longer sinus node recovery time in patients with the sick sinus syndrome was associated with a significantly greater asymptotic cycle length T_∞ ($p < 0.005$) and computed sinoatrial conduction time ($p < 0.05$). ΔT_1 , an index of the extent of suppression of the sinus node, was no different in controls and those with abnormal sinus node function. The common ratio q was also similar between the two groups.

COMPARISON OF RESULTS AFTER SINGLE EXTRASTIMULI AND AFTER FIXED RATE PACING

Indices indicating effects of a single extrastimulus, eight beats, and one minute of atrial pacing are compared in Table 3. The mean value of the first post-stimulation cycle length was not significantly different in either group of patients after a single extrastimulus or atrial pacing for eight beats or one minute.

Of all the computed indices, only ΔT_1 was significantly greater ($p < 0.05$) after fixed rate pacing (100 beats per minute) than after a single atrial extrastimulus. This held whether sinus node function was normal or abnormal. The common ratio q increased significantly ($p < 0.05$) with fixed rate pacing in those with the sick sinus syndrome but not in controls. The indices T_∞ and computed sinoatrial conduction time were not significantly different after the different methods of stimulation.

Discussion

We examined in detail sequences that followed all pacing modalities used in conventional assessment of sinus node function. The "normal" patients were not strictly a control group for patients with sick



Table 3 Comparison of computed indices after single extrastimuli and overdrive atrial pacing

	Single extrastimuli	8 beats pacing	Overdrive pacing (1 min, 100 bpm)	Overdrive pacing (1 min, 130 bpm)
Normal				
T_1 (ms)	939 (171)	990 (178)	1085 (126)	986 (211)
q	0.675 (0.155)	0.698 (0.136)	0.685 (0.090)	0.687 (0.100)
ΔT_1 (ms)	136 (78)	178 (51)	249 (131)	188 (144)
T_∞ (ms)	736 (175)	721 (111)	733 (75)	677 (111)
Computed SACT (ms)	103 (17)	97 (52)	92 (67)	96 (61)
Sick sinus syndrome				
T_1 (ms)	1212 (182)*	1269 (200)*	1415 (506)	1541 (707)
q	0.643 (0.155)	0.706 (0.101)	0.731 (0.087)	0.652 (0.174)
ΔT_1 (ms)	145 (143)	172 (112)	254 (130)	249 (131)
T_∞ (ms)	919 (175)*	1003 (187)*	887 (137)*	867 (148)*
Computed SACT (ms)	159 (67)*	159 (71)*	185 (114)*	178 (119)*

T_1 , first post-stimulation cycle length, q , ΔT_1 , and T_∞ , computed indices of automaticity; SACT, sinoatrial conduction time (computed from T_1 using model of sinus node recovery), * $p < 0.05$ by t test for comparison of grouped mean indices in those with normal sinus node function and those with sick sinus syndrome.

sinus syndrome, because they were significantly younger and aging itself affects sinus node function¹⁶; thus a case/control study with age matching is needed.

Although the methods proposed for indirect assessment of sinoatrial conduction time,^{10,11} are based on only the lengthening of the first post-stimulus interval after atrial extrastimulus and fixed rate atrial pacing for eight beats, they usually also reduce the prolongation of second and subsequent intervals. The time course of this ongoing depression closely resembles that seen after prolonged atrial pacing and may be attributed to depressed automaticity of the sinus node. This suggests that sinoatrial conduction time as calculated by these methods is in fact a compound measurement composed partly of sinoatrial conduction time and partly of depressed sinus node automaticity. We used a mathematical model of overdrive suppression to identify the two separate components in the overall sequence of post-pacing intervals. The model allows us to compare the extent to which each of the pacing methods individually influences sinoatrial conduction and sinus node automaticity. The model is not applicable to all patients since a few post-pacing sequences cannot be fitted to the model because of strong autonomic effects on the sinus node, spontaneous atrial activity, and sinoatrial exit block.

How valid is the model? It assumes that all sinus node cells follow the same process of recovery, that the anterograde sinoatrial conduction time of all cycles in the sequence is constant, and that there are no pacemaker shifts, or if these are present, that they contribute negligibly to the sinoatrial conduction time. There is evidence from animal experimentation that the cycle length changes seen after atrial extrastimuli relate to changes in the primary pacemaker location.¹⁷ Further, the atrial electrical

events do not correlate well with events within the sinus node.¹⁸ Even if the above assumptions are shown to be incorrect in man, certain conclusions can be drawn from this study which are most important in highlighting the limitations of widely used techniques of assessment.

CONVENTIONAL METHODS OF DETERMINATION OF SINOATRIAL CONDUCTION TIME ARE IMPURE

The derivation of sinoatrial conduction time from cycles that follow a single atrial extrastimulus or eight beats of fixed rate pacing assumes that the contribution of depression of automaticity is an insignificant part of the return cycle. The post-pacing sequences observed in this study strongly suggest that this does not hold. The results indicate that depression of automaticity either because of depression of the primary pacemaker, pacemaker shift,¹⁷ or both together, may contribute up to 50% of the prolongation of the return cycle over the pre-pacing cycle length. Although suppression of automaticity by atrial extrastimuli has been shown in both experimental animal preparations and in man¹¹ it has been considered to be of only minor importance.

Other factors affecting automaticity may also operate when sinoatrial conduction time is estimated by atrial pacing. At times, pacing at a cycle length within 30–50 ms of that of the sinus node may result in acceleration due to electronic interaction and shortening of action potential duration¹⁹ and isorhythmic sinoatrial dissociation.²⁰ Furthermore, computed sinoatrial conduction time more reliably differentiates between controls and those with sick sinus syndrome than do conventional indirect methods of estimation of sinoatrial conduction time. The

mean computed values for sinoatrial conduction time showed a 56 ms difference between sick sinus patients and controls. The difference derived conventionally from the same data was 29 ms. This difference is compounded by the much reduced standard deviation of the computed sinoatrial conduction time of the normal group (17 ms) as compared with the conventional sinoatrial conduction time (55 ms). Thus only four sick sinus patients could be identified by conventional methods, whereas nine were identified by the computational method.

SEQUENCES AFTER SINGLE ATRIAL EXTRASTIMULI AND FIXED RATE PACING ARE QUALITATIVELY SIMILAR AND DIFFER ONLY IN THE EXTENT OF SINUS NODE SUPPRESSION

Observations on the sequences that follow both single atrial extrastimuli and atrial pacing showed that most had a maximally extended first interval with a decline in the prolongation in subsequent cycles. The most obvious effect of prolonged pacing was greater suppression of automaticity (reflected by ΔT_1), and this effect occurred whether sinus node function was normal or abnormal. Other indices computed by fit to the model showed pronounced similarity. In particular, the different methods of stimulation gave the same mean computed sinoatrial conduction time. The asymptotic cycle length that followed recovery was no different with the various methods and probably reflects only resting sinus node automaticity.

SUPPRESSION OF THE SINUS NODE BY OVERDRIVE IS THE SAME IN PATIENTS WITH NORMAL AND ABNORMAL SINUS NODE FUNCTION

The only indices of automaticity which differed significantly between the two patients groups were resting cycle length and T_∞ (which as discussed may be primarily dependent on resting cycle length). As not only resting cycle lengths but also mean age were significantly different in those with normal and abnormal sinus node function, indices relating to this cycle length may have been less discriminatory if patients of similar ages had been compared.

In conclusion, this study suggests that previously used stimulation methods for electrophysiological testing of sinus node function (sinus node recovery time and sinoatrial conduction time derived from the first interval after atrial single extrastimuli or atrial pacing) are qualitatively similar and differ only in the extent of pacemaker suppression that they produce. The fact that they measure both sinoatrial conduction and sinus node automaticity may explain

their frequent failure to distinguish between normal and abnormal function, given the heterogeneous nature of bradyarrhythmias with which patients present. It might be expected that sinus node function will be better assessed by pure indices of automaticity or conduction, the latter obtained either directly by electrode recording¹²⁻¹⁴ or from application of simplified versions of the mathematical model.

We acknowledge the contribution of Dr Arieh Helfgott who developed the mathematical model and we thank Sister Lyn Bartlett, Mr R Blood, and Mrs Sue Love for their help with this study.

This work was supported by grants of the Life Insurance Medical Research Fund of Australia and New Zealand, the National Heart Foundation of Australia, and the Lions South Australian Heart Research Foundation.

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Preoperative and postoperative pulmonary function tests in patients with atrial septal defect and their relation to pulmonary artery pressure and pulmonary:systemic flow ratio

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SUMMARY Pulmonary diffusing properties and lung volumes were investigated in 44 patients with atrial septal defect, and in 30 of them preoperative and postoperative data were obtained. The patients were divided into three groups according to mean pulmonary artery pressure: ≤ 15 mm Hg (group 1), 16–29 mm Hg (group 2), and ≥ 30 mm Hg (group 3). Patients in groups 1 and 2 had a high carbon monoxide transfer test which became normal after surgical correction of their septal defect. In group 3, the carbon monoxide transfer test was normal both before and after operation. As mean pulmonary artery pressure increased there was a progressive reduction in both forced expiratory volume in one second and vital capacity. Patients in group 3 had a low forced expiratory volume in one second, a low vital capacity, and a reduced forced expiratory volume in one second:vital capacity ratio. These abnormalities were not corrected by surgical closure of the septal defect.

Formulas were derived from the lung function data, to predict the mean pulmonary artery pressure and the pulmonary:systemic flow ratio. The values predicted when these two formulas were applied to data obtained for patients in this study correlated well with measured values.

In most studies the carbon monoxide transfer test (T_LCO) has been found to be increased in patients with atrial septal defect.^{1–6} It has been suggested that this change is due to an increase in capillary blood volume.^{7,8} A study by De Troyer *et al* showed that patients with atrial septal defect complicated by pulmonary hypertension had reduced lung volumes and increased airway resistance.⁶

There have been few studies measuring T_LCO and lung volumes after surgical correction of atrial septal defects. Bucci *et al* reported seven patients with atrial septal defect in whom T_LCO and capillary blood volume returned to normal after operation.⁹ The present study was designed to investigate the effects on pulmonary function of surgical closure and also to determine whether pulmonary function tests could be used to predict mean pulmonary artery pressure

or the pulmonary:systemic flow ratio in patients with atrial septal defect.

Patients and methods

Forty four consecutive patients (aged 11–60 years) with atrial septal defect presenting over a three year period were studied; 43 had ostium secundum defects and one had an ostium primum defect. All patients with additional cardiac lesions were excluded, and no subject had evidence of primary pulmonary disease. In each case right heart catheterisation was performed to confirm the diagnosis, the mean pulmonary artery pressure was measured, and the pulmonary:systemic flow ratio was calculated by oximetry.¹⁰

The pulmonary function tests were all carried out with the patient in the sitting position. Lung volumes were measured with a conventional water-sealed spirometer (Gould-Goddard expirograph type 16000). The total lung capacity was measured with the same apparatus, by means of a steady-state

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helium dilution method. The results were compared with predicted values.¹¹⁻¹⁴ The Morgan transfer test model C, a single-breath technique, was used to measure the lung carbon monoxide uptake. The predicted values for T_LCO are those of Morgan.¹⁵ In all cases, the interval between pulmonary function testing and cardiac catheterisation was less than six weeks. A control group of 50 subjects who were attending a gastroenterology outpatient clinic had the same pulmonary function measurements taken during the same period of time.

Of the 44 patients in the study, 30 had pulmonary function tests repeated after surgical correction of their atrial septal defect. The remaining 14 patients included five who did not have operation (three had small shunts and two had severe pulmonary hypertension) and nine in whom repeat pulmonary function tests were not performed.

The observed and predicted values for lung volumes and T_LCO were compared by the paired *t* test. Statistical analysis by multiple linear regression was used to investigate the relation between pulmonary function tests and data obtained at cardiac catheterisation.

Results

The 44 patients in the study were divided into three groups according to their mean pulmonary artery pressure: group 1 (≤ 15 mm Hg), group 2 (16–29 mm Hg), and group 3 (≥ 30 mm Hg). These groups are similar to those studied by De Troyer *et al.*⁶ Their age, smoking habits (a "smoker" had smoked five or more cigarettes each day for at least the two previous years), and haemodynamic characteristics are shown in Table 1. The frequency of smoking in each of the three groups was similar.

Table 2 gives preoperative pulmonary volumes and T_LCO values. There was a progressive reduction in forced expiratory volume in one second and vital capacity as mean pulmonary artery pressure increased; in groups 2 and 3 values were significantly (paired *t* test) lower than predicted. There were significant inverse correlations of forced expiratory volume in one second ($r = -0.45$; $p < 0.01$) and vital

capacity ($r = -0.32$; $p < 0.05$) with mean pulmonary artery pressure. The ratio of forced expiratory volume in one second:vital capacity also correlated inversely ($r = -0.52$; $p < 0.001$) with mean pulmonary artery pressure (Fig. 1). The total lung capacity did not differ significantly from predicted values in any of the groups. There was a striking increase in T_LCO in groups 1 and 2 ($p < 0.001$), whereas patients with a mean pulmonary artery pressure of ≥ 30 mm Hg had a normal value. The T_LCO showed a significant inverse correlation ($r = -0.52$; $p < 0.001$) with mean pulmonary artery pressure (Fig. 2), and Fig. 3 shows that mean pulmonary artery pressure increased with age ($r = 0.66$; $p < 0.001$).

Table 3 shows the pulmonary volumes and T_LCO measured after surgical correction of the atrial septal defect and the interval between operation and lung function testing in 30 patients. The reduced forced expiratory volume in one second and vital capacity associated with a mean pulmonary artery pressure ≥ 30 mm Hg did not become normal after operation; they remained significantly lower than predicted ($p < 0.01$). The pronounced increase in T_LCO noted in groups 1 and 2 before operation became normal postoperatively.

Backward stepwise multiple linear regression showed that mean pulmonary artery pressure correlated positively with age (Fig. 3) and inversely with T_LCO (Fig. 2). A formula was derived from these variables to predict the mean pulmonary artery pressure (P_{pa}):

$$\text{Predicted } P_{pa} = k_1 \times \text{age} + \frac{k_2}{T_LCO} - k_3$$

with age in years, T_LCO as percentage of predicted, and k_1 , 0.483, k_2 , 3246, and k_3 , 19.1. This regression was highly significant ($p < 0.001$, $R^2 = 63\%$) and allowed good prediction in most cases (Fig. 4). Within the measured range of mean pulmonary artery pressure (10–45 mm Hg) the predicted values are even more reliable. The addition of forced expiratory volume in one second and vital capacity to the formula did not improve the degree of prediction of mean pulmonary artery pressure.

Backward stepwise multiple linear regression

Table 1 Data on 44 patients studied with atrial septal defect (mean (SD))

	Age (years)	Smokers (%)	P_{pa} (mm Hg)	P:S flow ratio
Group 1 (n = 16)	21.7 (9.1)	31.3	12.6 (2.3)	2.72 (0.67)
Group 2 (n = 13)	32.3 (12.6)	30.8	20.7 (2.6)	3.47 (1.13)
Group 3 (n = 15)	47.4 (6.2)	33.3	39.3 (11.5)	2.75 (1.11)

P_{pa} , mean pulmonary artery pressure.

P:S flow ratio, ratio between pulmonary and systemic blood flows.

Table 2 Preoperative pulmonary volumes and diffusing properties in 44 patients with atrial septal defect (mean (SD))

	FEV ₁ (l)	VC (l)	FEV ₁ /VC (%)	TLC (l)	T _L CO (ml/min/mm Hg)
Group 1 (n=16)	2.81 (0.71) (2.86 (0.44))*	3.44 (0.91) (3.76 (0.60))	82.5 (7.2)† (76.2 (0.8))	4.96 (0.94) (4.79 (0.98))	33.8 (6.1)‡ (26.1 (4.1))
Group 2 (n=13)	2.39 (0.83)† (2.77 (0.54))	3.02 (1.13)† (3.65 (0.72))	79.5 (6.5) (75.9 (0.6))	4.59 (1.40) (4.88 (1.05))	35.7 (6.5)‡ (26.4 (4.4))
Group 3 (n=15)	1.74 (0.73)† (2.83 (0.57))	2.54 (0.87)† (3.72 (0.76))	67.7 (9.2)† (75.9 (1.1))	4.62 (1.27) (4.58 (0.90))	27.0 (6.9) (24.9 (4.1))

FEV₁, forced expiratory volume in one second; VC, vital capacity; TLC, total lung capacity; T_LCO, carbon monoxide transfer test.

*Figures in parentheses are predicted values (mean (SD)). †Significantly different from predicted ($p < 0.01$). ‡Significantly different from predicted ($p < 0.001$).

showed that the pulmonary:systemic flow ratio did not correlate with the age of the patient, the forced expiratory volume in one second, or the vital capacity when these were expressed as a percentage of predicted values ($r = -0.16$, $r = -0.15$, $r = -0.14$ respectively). There was, however, a significant correlation between pulmonary:systemic flow ratio and T_LCO expressed as percentage of predicted ($r = 0.45$, $p < 0.005$) (Fig. 5). It was interesting to note that a pulmonary:systemic flow ratio of 4 or 5 produced T_LCO values rising to 160–170% of predicted, since similar T_LCO measurements have been obtained in normal subjects on maximum exertion, when cardiac output is four or five times that of normal.¹⁶ T_LCO was used to derive a formula to predict the ratio between pulmonary and systemic blood flow (P:S flow ratio): Predicted $\log_{10}$ P:S flow ratio = $k_a \log_{10}$ T_LCO - k_b ; where T_LCO is percentage of predicted, k_a , 1.015; and k_b , 1.673. Again, this regression was highly significant ($p < 0.001$, $R^2 = 40\%$) (Fig. 6). When this formula was used to predict a pulmonary:systemic flow ratio of > 2 , or < 2 , the prediction was correct in 38 of the 44 cases studied. The horizontal

and vertical lines in Fig. 6 correspond to a pulmonary:systemic flow ratio of 2, predicted and measured respectively.

The size of the shunt in patients with atrial septal defect is also reflected by the pulmonary artery oxygen saturation. It is noteworthy that T_LCO, expressed as percentage of predicted, correlated significantly ($r = 0.60$; $p < 0.001$) with the pulmonary arterial oxygen saturation (Fig. 7).

The pulmonary volumes and T_LCO measured in the control group did not differ significantly from predicted values.

Discussion

The increase in T_LCO in some patients with atrial septal defect is well established,^{1–6} and occurs as a consequence of an increase in capillary blood volume.^{7,8} In the study by De Troyer *et al* of 24 patients with atrial septal defect, T_LCO was not increased in patients with mean pulmonary artery pressure > 25 mm Hg.⁶ The finding of a normal or low T_LCO in the presence of pulmonary hypertension has also been

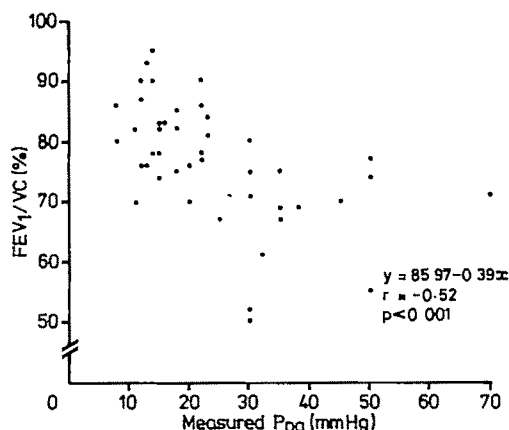


Fig. 1 Ratio of forced expiratory volume in one second to vital capacity (FEV₁:VC %) versus measured mean pulmonary artery pressure (P_{pa}) in 44 patients with atrial septal defect.

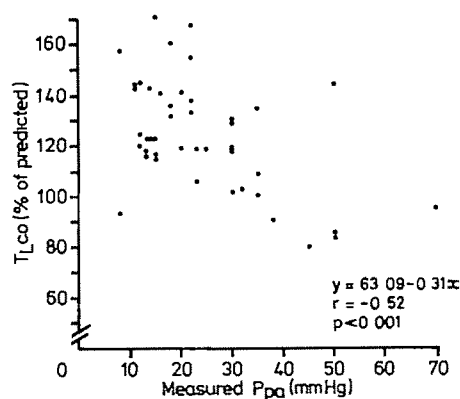


Fig. 2 Carbon monoxide transfer test (T_LCO) as percentage of predicted versus measured mean pulmonary artery pressure (P_{pa}) in 44 patients with atrial septal defect.

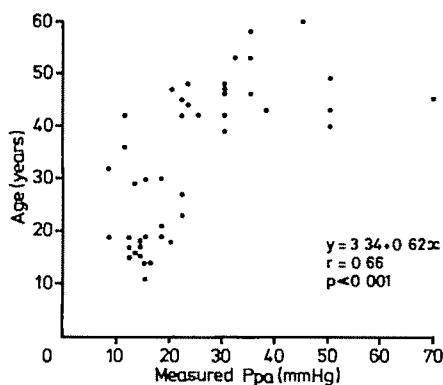


Fig. 3 Relation between age and measured mean pulmonary artery pressure (P_{pa}) in 44 patients with atrial septal defect.

described by Burgess.⁵ The results from our larger study therefore accord with those of most other investigators, in that patients with a mean pulmonary artery pressure ≥ 30 mm Hg had a normal T_LCO . It has been suggested^{5,9} that the chronic increase in pulmonary blood flow results in the opening of previously closed pulmonary capillaries and possibly distension of open capillaries and that this increases capillary blood volume and T_LCO . The presence of pulmonary hypertension, however, and an increased pulmonary vascular resistance limits the increase in capillary blood volume and T_LCO . Bucci *et al* have suggested that there is some active regulation of the resistance of the prepulmonary and postpulmonary capillary vessels which affects capillary blood volume.⁹

There was a progressive fall in both forced expiratory volume in one second and vital capacity as mean pulmonary artery pressure increased. In patients with a mean pulmonary artery pressure of ≥ 30

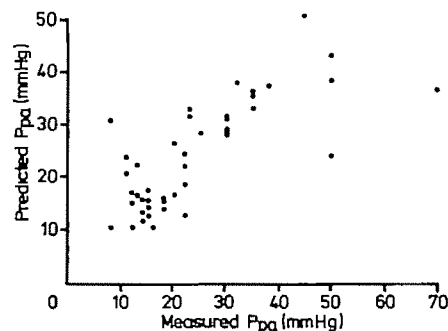


Fig. 4 Measured versus predicted mean pulmonary artery pressure (P_{pa}) from $k_1 \times \text{age} + k_2/T_LCO - k_3$. T_LCO is carbon monoxide transfer test.

mm Hg, the forced expiratory volume in one second:vital capacity ratio was significantly lower than predicted. As there was no significant difference in the percentage of smokers in each group, the changes are unlikely to be the consequence of smoking habits. These findings are consistent with those of De Troyer *et al* who described reduced lung volumes and increased airway resistance in patients with mean pulmonary artery pressure > 25 mm Hg.⁶ They reported a progressive decrease in lung compliance with increasing pulmonary hypertension, due to vascular engorgement. Their results also suggested that the obstruction to airflow was mainly localised in the small peripheral bronchioles. It has been postulated¹⁷ that competition for space between vessels and airways within the bronchovascular sheaths increases the resistance of the small airways. Other studies in children with heart disease¹⁸ and in adults¹⁹ support this theory.

Bucci *et al* reported seven patients with atrial septal defect in whom T_LCO and capillary blood volume decreased to within normal limits after surgical cor-

Table 3 Preoperative and postoperative pulmonary volumes and diffusing properties in 30 patients with atrial septal defect (mean (SD))

	FEV_1 (l)	VC (l)	T_LCO (ml/min/mm Hg)	Months after operation
Group 1 (n=11):				
Preoperative	2.85 (0.62)	3.55 (0.80)	34.3 (5.3)†	
Postoperative	3.02 (0.79)	3.46 (0.75)	27.9 (5.4)	42
	(2.81 (0.44))*	(3.69 (0.58))	(26.5 (4.6))	
Group 2 (n=9)				
Preoperative	2.43 (0.90)	3.14 (1.28)	35.0 (7.6)†	
Postoperative	2.57 (1.13)	3.41 (1.55)	27.6 (7.6)	39
	(2.81 (0.55))	(3.70 (0.74))	(25.8 (4.5))	
Group 3 (n=10)				
Preoperative	1.89 (0.84)†	2.73 (0.98)†	29.8 (6.5)	
Postoperative	1.96 (0.72)†	2.80 (0.99)†	24.9 (7.1)	33
	(2.92 (0.60))	(3.84 (0.80))	(25.4 (4.2))	

Abbreviations are given in footnote to Table 2.

*Figures in parentheses are predicted values (mean (SD)). † Significantly different from predicted ($p < 0.01$). ‡ Significantly different from predicted ($p < 0.001$)

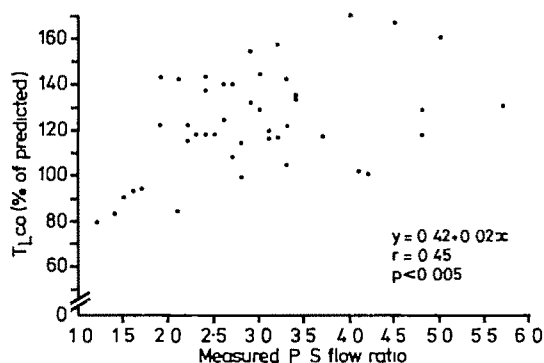


Fig. 5 Carbon monoxide transfer test (T_LCO) as percentage of predicted versus pulmonary:systemic flow ratio (P:S flow ratio) in 44 patients with atrial septal defect.

rection of their cardiac abnormality.⁹ Auchincloss *et al*² reported two cases in which T_LCO became normal after closure of the defect. In our study, 30 patients had T_LCO measured before and after operation. In the 20 cases with mean pulmonary artery pressure < 30 mm Hg the high T_LCO values became normal after surgical correction; in the remainder with mean pulmonary artery pressure $\geq$ 30 mm Hg, T_LCO was within normal limits before and after operation. These results suggest that the re-establishment of normal haemodynamic conditions is followed by a return towards normal of the pulmonary capillary bed. It is of interest that in patients with mean pulmonary artery pressure $\geq$ 30 mm Hg, the low forced expiratory volume in one second and vital capacity did not return to normal after surgical correction of

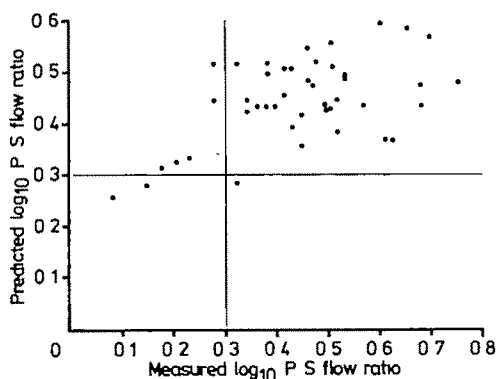


Fig. 6 Measured versus predicted ratio between pulmonary and systemic blood flow (P:S flow ratio). Predicted $\log_{10}$ P:S flow ratio = $k_a \times \log_{10} T_LCO - k_b$. T_LCO is carbon monoxide transfer test.

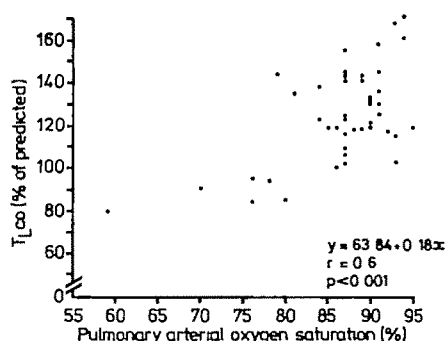


Fig. 7 Carbon monoxide transfer test (T_LCO) as percentage of predicted versus pulmonary arterial oxygen saturation in 44 patients with atrial septal defect.

the atrial septal defect. This suggests that there is some permanent irreversible change in the small airways and lung parenchyma as a consequence of long-standing increased pulmonary blood flow.

The formula derived to predict mean pulmonary artery pressure involved two variables—age (years) and T_LCO (percentage of predicted). The regression was highly significant and allowed good prediction of mean pulmonary artery pressure particularly within the measured range of 10–45 mm Hg. The ratio of pulmonary to systemic flow is generally considered to be the best overall indication of the haemodynamic importance of an atrial septal defect. Although a value of 2 or more is usually considered to indicate an important defect, the measurement is itself subject to error. When $\log_{10} T_LCO$ (as percentage of predicted) was used to predict $\log_{10}$ pulmonary:systemic flow ratio, the regression was highly significant. When the formula was used to predict whether the pulmonary:systemic flow ratio was > 2 or < 2 the prediction was correct in 86% of patients. The pulmonary arterial oxygen saturation, which reflects shunt size, also correlated with T_LCO expressed as a percentage of that predicted.

In recent years radionuclide angiography²⁰ and echocardiography²¹ have provided information in patients with atrial septal defect that previously could be obtained only by invasive techniques. It has been suggested that routine preoperative catheterisation may be unnecessary when typical clinical features of an uncomplicated atrial septal defect are confirmed by cross sectional echocardiography and, when indicated, other non-invasive tests.^{22, 23} It is possible that the techniques we describe for predicting mean pulmonary artery pressure and the pulmonary:systemic flow ratio could provide useful additional information in the assessment and follow up of patients with atrial septal defect and thereby

increase confidence in management decisions made without cardiac catheterisation. At this stage, however, the formulas have only been tested on the population from which the predictions were derived.

We thank Dr C L Bray, Dr C Ward, and Dr D H Bennett for allowing us to study patients under their care; and Dr S S Chatterjee for the use of the respiratory physiology laboratory.

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Congenital heart malformations in the first year of life—a necropsy study

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SUMMARY The hearts of 291 babies with congenital heart disease who died before the age of one were examined systematically by sequential segmental analysis to determine the lesions that were present. There was an abnormal connection between the cardiac segments in one third of cases. Patent ductus arteriosus, which is usually a common defect, was not an important finding at necropsy, whereas common arterial trunk (a rare defect) was found in 10%. The clinical and necropsy incidence of complete transposition was similar to that reported in earlier studies. The incidence of some lesions present at necropsy (for example Fallot's tetralogy) has altered over the past 10 years. A decline in the frequency with which a lesion is detected at necropsy may indicate advances in treatment or differences in classification. The presence of additional lesions influences the prognosis and subcategorisation within the major defect groupings gave some insight into the cause of death in many of the cases.

In the West congenital heart disease is the most common cardiac condition of childhood. It may affect as many as 2% of livebirths^{1,2} and many babies with congenital heart disease die within the first few weeks of life. More die, with or without surgical intervention, before the end of their first year.

More specific classification of these cardiac lesions depends on a systematic approach to the diagnosis of congenital heart malformations, such as that proposed by Van Praagh.³ With some modifications⁴ we have used this approach to analyse a large series of necropsy cases aged one year and younger collected over the past ten years at this hospital.

Patients and methods

We studied 291 hearts from patients who died within the first year of life. These hearts comprised 72% of the 403 specimens that were collected by the Paediatric Cardiac Morphology Laboratory, Cardiothoracic Institute, University of London from October 1974 to October 1984. Most came from patients attending the Brompton Hospital, while a small proportion were referred from other centres in the United Kingdom.

The specimens were divided into two age groups—those aged <4 weeks and those aged from 4 weeks to one year.

We systematically examined each heart by a sequential segmental approach⁴ and noted any abnormal connections or arrangements of the cardiac segments. We then ascribed a primary diagnosis to each heart. Hearts which showed an absent left atrioventricular connection, with a main chamber of right ventricular morphology (classical mitral atresia) and hearts with an imperforate mitral valve were grouped with specimens having aortic atresia. This was so that our series could be compared with clinical series in which these conditions were combined. In hearts with multiple lesions the primary lesion was the one regarded as being of greatest morphological importance. In some cases these primary lesions were further categorised by subgroup.

The incidence of each lesion in both age groups was calculated as a percentage. This necropsy incidence was compared with the clinical incidence at the Brompton Hospital,⁵ and both these sets of data were then compared with data from other centres.^{6,7}

Results

Table 1 shows the sequential segmental arrangement and connections in the hearts that we examined. Two of the four specimens with left atrial

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Accepted for publication 10 September 1985

Table 1 *Sequential segmental arrangement and connections of hearts from 291 cases <1 year*

	No	%
Atrial arrangement:		
Normal (situs solitus)	276	95.2
Right atrial isomerism	11	3.8
Left atrial isomerism	4	1.4
Atrioventricular connection		
Concordant	246	84.5
Discordant	1	0.3
Biventricular ambiguous connection		
Left hand topology (l loop)	3	1.0
Right hand topology (d loop)	4	1.4
Double inlet		
Right ventricle	4	1.4
Left ventricle	4	1.4
Indeterminate ventricle	4	1.4
Absent right connection		
Dominant right ventricle	1	0.3
Dominant left ventricle	6	2.1
Indeterminate ventricle	1	0.3
Absent left connection		
Dominant right ventricle	16	5.5
Dominant left ventricle	1	0.3
Ventriculoarterial connection		
Concordant	174	59.8
Discordant	32	11.0
Double outlet		
Right ventricle	28	9.6
Left ventricle	4	1.4
Indeterminate ventricle	4	1.4
Single outlet		
Common arterial trunk	23	7.9
Pulmonary trunk	9	3.1
Aortic trunk	37	12.7

isomerism showed an ambiguous biventricular atrioventricular connection. Each case was connected to a ventricular mass having right hand topology (d loop). Five of the 11 cases of right atrial isomerism had ambiguous connections. Two cases had right hand ventricular topology and three had left hand topology (l loop). There was a univentricular atrioventricular connection in 37 specimens. There were 17 examples of absent left atrioventricular connection, of which 16 cases were classic mitral atresia. In each of these, the right atrium was connected to a dominant right ventricle. In the remaining case the right atrium drained to a dominant left ventricle.

Sixty per cent of the cases had concordant ventriculoarterial connections. There were discordant connections in 32 (11%) hearts. There were 36 (12.4%) specimens with double outlet connection. The remaining 69 (23.7%) cases had single outlet connections.

Thirteen primary lesions were identified; each accounted for more than 4% of the necropsy cases (Table 2). Each group was subdivided to give a more comprehensive view of the spectrum of malformations (Table 3). Data on surgical experience are also included. The most frequent condition found at necropsy in the first month of life was common arterial trunk. Fifteen (9.9%) of the 151 hearts

had this lesion (Table 3). Of the 15, five cases had the additional lesion of interruption of the aortic arch and a further two cases had other arch anomalies. Another two cases showed truncal valve incompetence. Total correction had been attempted in one case with interruption and in two other cases. This lesion also showed an appreciable incidence in the older group, accounting for 5.7% of hearts from those aged between one month and one year. Of the eight cases, three had truncal valve stenosis and one of these also had major accessory systemic-pulmonary collateral arteries. Another case had partial anomalous pulmonary venous connection and a fifth had arch hypoplasia. Four cases had undergone complete repair, after which one case developed atrioventricular heart block. A palliative operation had been performed on one heart in each age group; in the younger case the heart had additional interruption of the aortic arch and the older case had severe truncal valve stenosis.

In the younger age group the incidence of mitral and aortic atresia or both (9.9%) was considerable. There were 11 cases of mitral atresia; five had additional aortic stenosis and isthmal hypoplasia, and five had aortic atresia. Aortic atresia alone was seen in four cases all of which had mitral valve stenosis. Isolated aortic atresia was not seen in the older group and there were only five cases of mitral atresia—two with additional pulmonary atresia, one with double outlet right ventricle, and two with hypoplasia of the aortic arch. Three cases from each age group had had palliation.

Hearts with a univentricular atrioventricular connection (excluding classic mitral atresia)—that is those with no right/left atrioventricular connection and a double inlet ventricle—comprised 9.3% of the hearts of those who died during the first month of life. There was one case of classic tricuspid atresia, two cases of tricuspid atresia with complete transposition (both cases having aortic obstruction and isthmal hypoplasia), one case of absent right atrioventricular connection to an indeterminate ventricle with pulmonary atresia, one of absent right atrioventricular connection with the left atrium connecting to a dominant right ventricle; one of absent left atrioventricular connection with the right atrium connecting to a dominant left ventricle; three cases of double inlet left ventricle (two with aortic isthmal hypoplasia and double outlet left ventricle, the other with pulmonary atresia and right ventricular origin of the aorta); three cases of double inlet right ventricle (one with pulmonary atresia and two with atrial isomerism and its usual accompanying lesions), and two cases of double inlet to an indeterminate ventricle (both with atrial isomerism). Palliative procedures had been performed in six hearts. In addi-

Table 2 Necropsy incidence of the primary lesions found in the two age groups

	Incidence (%) newborn- 1 mth (n=151)	Incidence (%) 1 mth-1 yr (n=140)
Common arterial trunk	9.9	5.7
Arch interruption	8.6	1.4
Arch hypoplasia including discrete coarctation	9.3	7.1
Univentricular atrioventricular connection*	9.3	5.0
Complete transposition	7.3	10.0
Mitral atresia and aortic atresia or both	9.9	3.6
Pulmonary atresia with intact septum	7.3	7.2
Double outlet right ventricle	4.0	8.6
Anomalous pulmonary venous connection	7.3	7.2
Atrioventricular septal defect	3.3	15.0
Ventricular septal defect	4.6	5.0
Pulmonary atresia with ventricular septal defect	1.3	3.6
Fallot's tetralogy	0.6	4.3

*Excluding classic mitral atresia.

tion, 5% of hearts from the older group had univentricular atrioventricular connection. Of the seven hearts, only one case—with double inlet left ventricle—showed atrial isomerism. Pulmonary outflow tract obstruction was seen in two of three cases of classic tricuspid atresia. There were two cases of double inlet to a solitary and indeterminate ventricle; one of these also had double outlet from the solitary ventricle and complete correction had been attempted. There was one example of double inlet right ventricle. Four cases had had palliative surgery.

The incidence of hypoplasia of the aortic arch in the younger group (9.3%) resembled that of univentricular atrioventricular connection. There were 14 cases in total, eight of which had associated ventricular septal defects. Discrete coarctation occurred in four cases, coarctation with tubular hypoplasia in two, and tubular hypoplasia alone in eight cases. Six of the cases had aortic outflow tract obstruction (Fig. 1a) and a further two cases had a bicuspid aortic valve. The incidence of arch hypoplasia was also high (7.1%) in the older age group. Six of the 10 hearts had discrete coarctation. Of these, two had left ventricular outflow tract obstruction, one had a bicuspid aortic valve, one a persistent left superior caval vein, and one had endocardial fibroelastosis. The remaining four hearts with tubular hypoplasia all had outflow tract obstruction and a ventricular septal defect.

Thirteen cases (8.6%) of interrupted aortic arch were to be seen in the younger age group. All but one case also had a ventricular septal defect. Eight cases had some obstruction to the subaortic outflow tract (Fig. 1b) and seven hearts had undergone total correction of the malformation. In contrast, arch interruption occurred only twice (1.4%) in the 140 cases aged between one month and one year. One case had a subaortic ventricular septal defect and

double outlet left ventricle and the other had an aortopulmonary window. In both cases surgical correction had been attempted.

The incidence of pulmonary atresia with intact septum and anomalous pulmonary venous connection was 7% in both age groups. Four of the eleven younger cases of pulmonary atresia with intact septum had Ebstein's malformation of the tricuspid valve. Three of the eleven had dilated, thin-walled right ventricles (Fig. 2a), while the remaining eight had small ventricular cavities resulting from gross trabecular hypertrophy or ventricular hypoplasia (Fig. 2b). Of the 10 cases in the older group, two had dysplastic and incompetent tricuspid valves and eight had right ventricular cavities which were obliterated by trabecular hypertrophy. All had been treated by palliative procedures. There were eleven cases of anomalous pulmonary venous connection in the group less than one month old. Five cases had an infradiaphragmatic anomalous connection. In contrast, none of the 10 cases aged between one month and one year showed an infradiaphragmatic connection.

Complete transposition was also important in the younger and older age groups, with an incidence of 7.3% and 10.0% respectively. Three of the eleven postnatal cases had associated coarctation or isthmal hypoplasia. In all, palliative surgery was performed on nine cases and total correction had been attempted on twelve.

The incidence of atrioventricular septal defect was fairly low (3%) in the younger age group. It was the most important of all the lesions in the older group (15%), however. Twenty two of the 26 cases had associated major complicating lesions—severe right ventricular dominance in three (Fig. 3); double outlet right ventricle in three; arch hypoplasia in six; pulmonary atresia in two; and left ventricular outflow tract obstruction in four. Surgery had been

Table 3 Classification and subclassification of lesions found at necropsy and the operations performed in these cases

Lesion	< 1 mth			1 mth-1 yr			Associated conditions
	No	Surgery	Palliation	No	Surgery	Palliation	
Common arterial trunk	10	2	—	8	4	1	Valve incompetence stenosis (5)
+ interruption	5	1	1	0	—	—	
Arch interruption	1	—	—	1	1	—	AP window (1)
+ VSD	4	3	—	0	—	—	
+ VSD and LVOTO	8	4	—	1	1	—	DOLV (1)
Coarctation	1	1	—	3	3	—	AVSD (1)
+ LVOTO	2	1	—	2	2	—	Arch hypoplasia (1)
+ VSD	3	1	—	1	1	—	Arch hypoplasia (1), ASD (1), VA discordance and RVOTO (2)
Arch hypoplasia	3	2	—	0	—	—	
+ VSD	5	2	—	4	4	—	LVOTO (7)
Ventricular septal defect	5	—	2	3	1	2	Mild arch hypoplasia (6); multiple defects (2)
+ LVOTO	2	—	1	2	2	—	
+ RVOTO	0	—	—	2	2	—	
Mitral atresia	4	—	—	2	—	1	
+ aortic atresia	5	—	1	0	—	—	Aortic stenosis (5)
+ pulmonary atresia	0	—	—	2	—	1	
+ DORV	2	—	2	1	—	1	Aortic stenosis (2)
Aortic atresia with mitral stenosis	4	—	—	0	—	—	
Pulmonary atresia	3	—	—	2	—	2	Ebstein's (2), incompetent tricuspid valve (3)
+ dilated RV	8	—	3	8	—	8	Ebstein's (2), incompetent tricuspid valve (2)
+ small RV	6	1	3	9	2	2	Arch hypoplasia (5)
Double outlet RV	0	—	—	3	3	—	
+ RVOTO	0	—	—	3	3	—	
Anomalous PV connection							
Infradiaphragmatic	5	4	1	0	—	—	
Supradiaphragmatic	5	2	—	7	7	—	
Unknown	1	—	—	3	—	1	
Univentricular AV connection							
Absent right	5	—	4	3	—	2	TGA (3), DOLV (1), RVOTO (2), pulmonary atresia (1)
Absent left	1	—	—	0	—	—	
Double inlet LV	2	—	1	0	—	—	DOLV (2)
+ pulmonary atresia	1	—	—	1	—	1	Right isomerism (1)
Double inlet RV	0	—	—	1	—	—	DORV (1)
+ RVOTO	3	—	1	0	—	—	Pulmonary atresia (2), DORV (1)
Double inlet indeterminate ventricle	2	—	—	2	1	1	Right isomerism (2)
Atrioventricular septal defect	2	—	—	15	10	—	Arch hypoplasia (6), RV dominance (3), mitral stenosis (2), hypoplastic RV (1), anomalous PV connection (1)
+ LVOTO	3	—	—	1	1	—	TGA (1)
+ pulmonary atresia	1	—	1	1	—	—	
+ DORV	0	—	—	3	2	—	
Pulmonary atresia + VSD							
+ ductal supply	2	—	2	4	—	2	Aortic override (2)
+ MAPCAs	0	—	—	1	—	1	
Tetralogy of Fallot	1	—	1	6	5	1	Aberrant PA (2), DORV (1)
Complete transposition	11	3	5	14	9	4	Mild arch hypoplasia (4)

AP, aortopulmonary; ASD, atrial septal defect; AVSD, atrioventricular septal defect; DOLV, double outlet left ventricle; DORV, double outlet right ventricle; LV, left ventricle; LVOTO, left ventricular outflow tract obstruction; MAPCAs, major accessory pulmonary collateral arteries; PA, pulmonary artery; PV, pulmonary venous; RV, right ventricle; RVOTO, right ventricular outflow tract obstruction; TGA, transposition of the great arteries; VA, ventriculoarterial; VSD, ventricular septal defect.

performed mainly on the older group; 13 of the 21 having had attempted total correction.

Double outlet right ventricle was found in 4% of the younger group and 8.6% of the older group. Three of the six younger hearts also had arch hypoplasia; only one had been repaired. The remaining three cases had had palliative procedures. Of the twelve cases in the older group, six had sub-pulmonary ventricular septal defects. Of these three

had severe right ventricular subaortic outflow tract obstruction and underwent attempted correction. A further two cases had surgical correction and palliation was performed on another two.

Fallot's tetralogy was not an important finding in the younger group. There were six cases in the age group one month to one year. Two of these had additional malformations of the aortic arch. Another had a narrow pulmonary trunk and double outlet

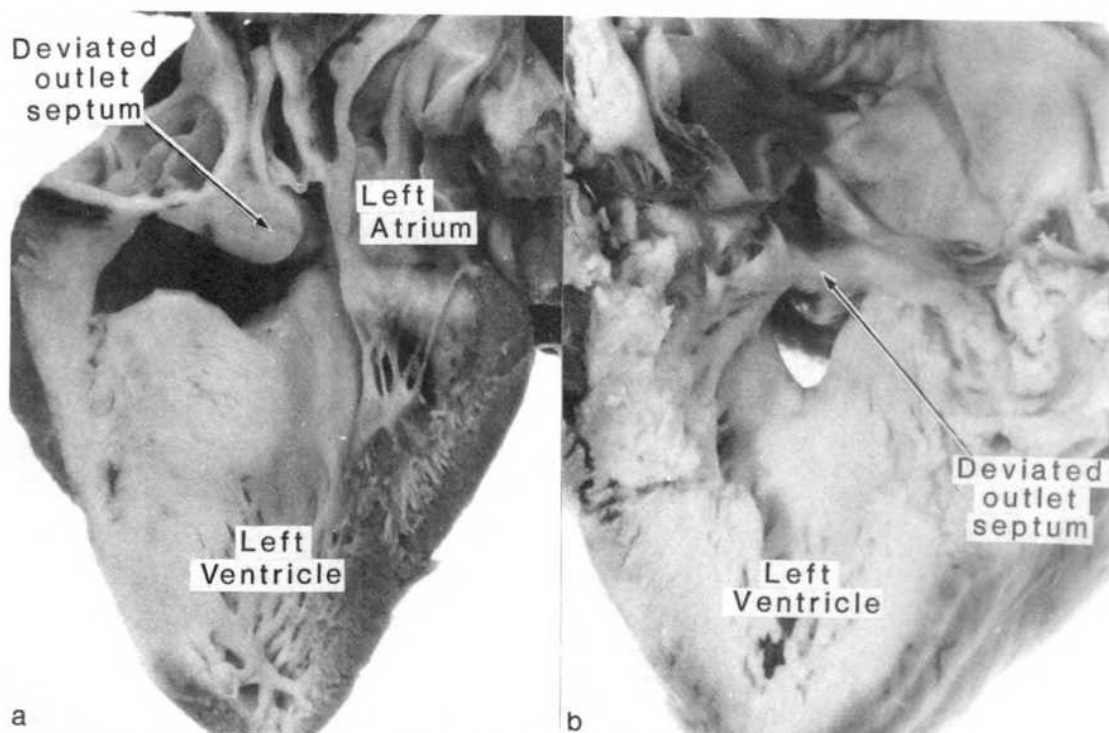


Fig. 1 Malalignment ventricular septal defect resulting in subaortic outflow tract obstruction in (a) aortic arch hypoplasia and (b) interrupted aortic arch.

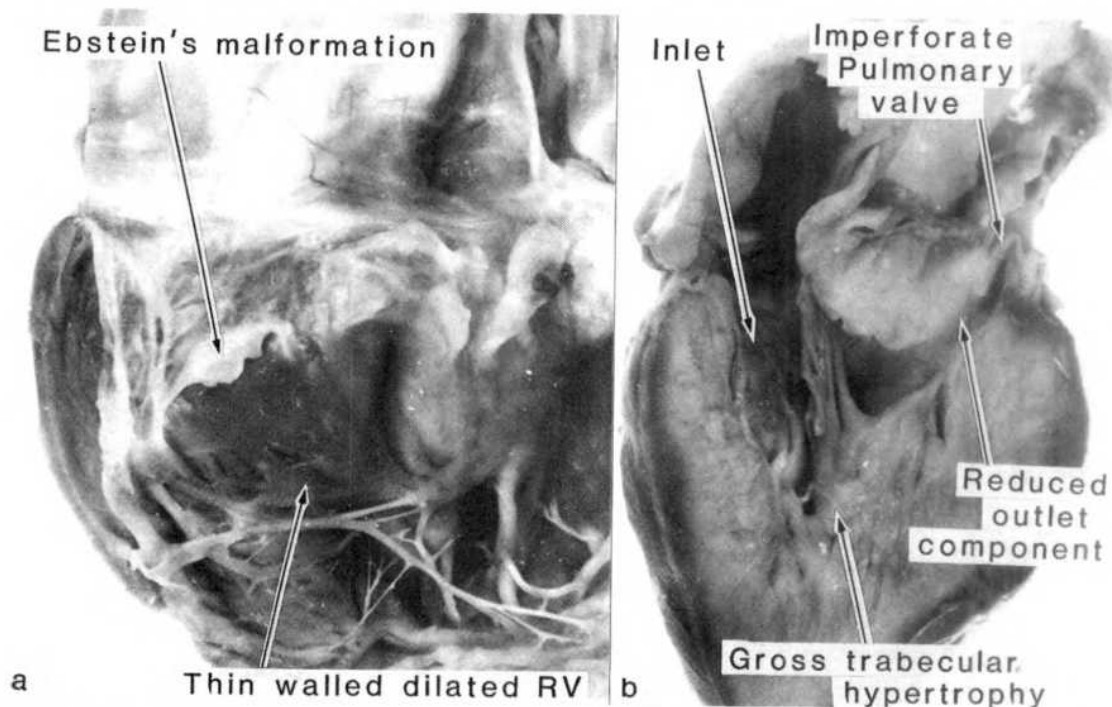


Fig. 2 The two morphological patterns of pulmonary atresia with intact septum. (a) Dilated thin walled right ventricle (RV) associated with Ebstein's malformation of the tricuspid valve. (b) Gross trabecular hypertrophy causing virtual obliteration of the apical trabecular and outlet components.

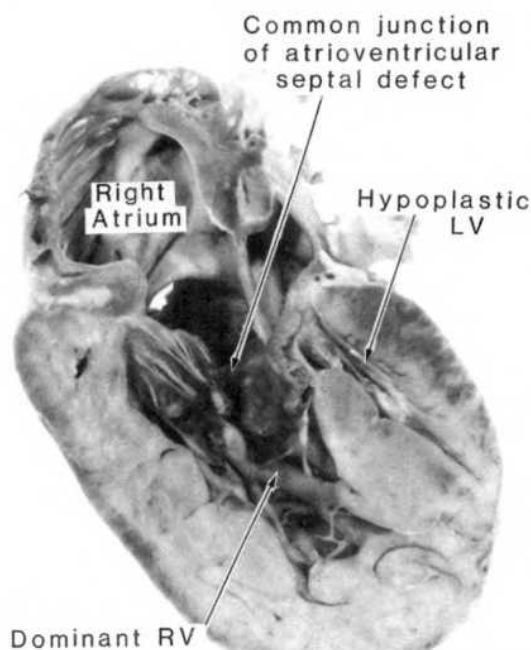


Fig. 3 An atrioventricular septal defect with an additional major complicating lesion, in this case severe right ventricular dominance. RV, right ventricle; LV, left ventricle.

right ventricle, a fourth had a bicuspid pulmonary valve, and severe right ventricular outflow tract obstruction was seen in a fifth. Total correction was attempted in five cases, while the case with a narrow pulmonary trunk had a palliative procedure.

Pulmonary atresia with ventricular septal defect was seldom seen in the younger group. Only two of a total of 151 hearts from those aged <4 weeks had this lesion compared with five of the 140 older cases. Both of the younger cases showed a ductal pulmonary blood supply while at least one of the older cases was known to have had major systemic-pulmonary collateral arteries.

The frequency of isolated ventricular septal defect was similar in both groups although it was not a dominant lesion in either. Of the 14 hearts with this defect five had had repair of the defect and five had had palliative procedures. In four of the seven younger cases there was mild arch hypoplasia and another two had left ventricular outflow obstruction caused by malalignment of the ventricular septum. Left ventricular outflow tract obstruction was seen in two of the seven older cases and right ventricular outflow tract obstruction in a further two.

The remainder of the 291 hearts had miscellaneous lesions such as malformations of the valve leaflets, coronary artery anomalies, cardiomyopathy, and so on.

Discussion

Necropsy cases in this study came mainly from one centre in the United Kingdom specialising in thoracic medicine. As such, it is a highly selected group of cases and it would be wrong to assume that the incidence of lesions seen here can be extrapolated to that in the population as a whole. In addition, not all the patients who die in our centre come to necropsy. It is thus impossible to calculate mortality figures from clinical and necropsy incidence data. A better estimate of this can be obtained from studies such as that recently reported by Samanek *et al.*⁸ in which all the stillbirths and children dying in a specified area of Czechoslovakia underwent necropsy. We can, none the less, compare our series with the Czech investigation and with those from centres similar to our own and from these data infer a trend of lesion incidence and prognosis.

Studies based on clinical experience have estimated that between a third and two thirds of children with congenital heart disease who die do so within the first year of life.^{19,10} Recent studies have shown that nearly as many died within the initial four weeks of life as did in the subsequent 48 weeks.¹¹ Our investigation has shown similar results: about a third of our hearts were from patients aged under a month at death, a third were under a year, and the remainder were from children aged over a year. Although we cannot say categorically that the heart defect was the cause of death it was considered the main contributing factor in all cases. Analysis of the results shows that there are two critical periods for the child born with a congenital heart defect. The first is undoubtedly the first month of life, during which time the arterial duct normally becomes occluded. Patients with defects which are duct dependent present with clinical symptoms and die at this time. Defects such as double outlet right ventricle and atrioventricular septal defect, however, do not present until the pulmonary vascular resistance falls at the end of the first month.

Some interesting points emerge from a comparison between necropsy data and the clinical incidence at our centre (Table 4). Firstly, persistent patency of the arterial duct (which is found in 10–11% in children born with congenital heart disease^{1,12}) had a clinical incidence of 6% and a necropsy incidence of <1%. The results resemble those found at other centres (Table 5). They could be taken to indicate that an anatomically patent duct is not a particularly lethal lesion. Or alternatively, current management of this condition may be very successful. Secondly, "isolated" ventricular septal defect, the most common lesion to present clinically

Table 4 *A comparison of the clinical incidence (Brompton Hospital) and the necropsy incidence in a series of hearts from patients < one year old*

Lesion	Clinical incidence 1973-82 (n = 1653)	Necropsy incidence 1974-84 (n = 291)
Ventricular septal defect	15.4	4.8
Complete transposition	10.9	8.6
Coarctation and hypoplasia	10.5	8.3
Tetralogy of Fallot	9.9	2.4
Persistent arterial duct	6.3	0.6
Atrioventricular septal defect	3.9	8.9
Pulmonary stenosis	3.0	—
Pulmonary atresia with intact septum	1.9	7.2
Anomalous pulmonary venous connection	3.6	7.2
Tricuspid atresia	4.7	7.2*
Univentricular atrioventricular connection	4.3	
Mitral atresia and/or aortic atresia	—	6.9
Double outlet right ventricle	3.0	6.2
Common arterial trunk	2.1	7.9
Atrial septal defect	0.5	—
Arch interruption	—	5.2

*Excluding classic mitral atresia.

Table 5 *A comparison of clinical data reported by four centres*

Lesion	Clinical incidence Brompton 1973-82 (n = 1653)	Diagnostic frequency NERICP ^a 1969-74 (n = 2381)	Keith et al ⁷ 1967 (n = 1380)	Lesion incidence Bohemian study 1952-79 (n = 2257)
Ventricular septal defect	15.4	15.7	26.0	22.6
Complete transposition	10.9	9.9	8.8	5.3
Fallot's tetralogy	9.9	8.9	6.8	—
Coarctation	10.5	7.5	4.1	5.2
Hypoplastic left heart	3.7	7.4	2.9	4.7
Persistent arterial duct	6.3	6.1	7.2	10.2
Atrioventricular septal defect	3.9	5.0	4.2	4.2
Pulmonary stenosis	3.0	3.3	—	4.7
Pulmonary atresia with intact septum	1.9	3.1	0.7	2.6
Atrial septal defect	0.5	2.9	3.3	3.6
Tricuspid atresia	4.7	2.6	3.2	4.1
Univentricular atrioventricular connection	4.3	2.4	—	—
Aortic stenosis	1.1	1.9	13.0*	2.4
Double outlet right ventricle	3.0	1.5	0.3	2.7
Common arterial trunk	2.1	1.4	1.8	1.7
Anomalous pulmonary venous connection	3.6	2.6	1.2	1.6

*Includes aortic atresia and mitral valve stenosis and atresia.
NERICP, New England Regional Infant Cardiac Program.

(with an incidence of > 15%) and in the Czech necropsy series (an incidence of 22%⁸) was found in only 5% of our necropsy cases. Moreover, the incidence was 5% in both age groups, whereas more than 80% of the clinical cases do not present until the pulmonary vascular resistance falls. This probably reflects the current policy of treating infants at local cardiac centres, with only serious cases being referred to national centres. The referral of serious cases to our hospital could account for the higher frequency of this lesion in the younger group and for the increased incidence at necropsy when compared with the New England study (Table 6). Thirdly, common arterial trunk, double outlet right ventricle, total anomalous pulmonary venous connection, and pulmonary atresia with intact septum—all of which

have a clinical incidence of less than 5%—were more commonly seen at necropsy. Fourthly, arch malformations, complete transposition, and univentricular atrioventricular connection (which have a low natural incidence) are the most frequently referred complex congenital heart malformations and are also dominant in the necropsy material. The fact that they remain dominant despite surgical intervention in more than half of the older patients under one year is disturbing. Fifthly, the clinical incidence of aortic stenosis and pulmonary stenosis is low and these conditions are not found at necropsy. Finally, we found that one third of our cases either had a major abnormality in the arrangement of the major cardiac segments^{3,4} or abnormal connections at at least one of the junctions.

Table 6 A comparison of data from three necropsy series

Lesion	Brompton 1974-84 (n = 291)	NERICP series 1969-74 (n = 900)	Bohemian study 1952-79 (n = 1090)
Univentricular atrioventricular connection	7.2*	5.7	4.7
Complete transposition	8.6	10.3	9.8
Arch interruption	5.2	2.1	0.6
Arch hypoplasia including coarctation	8.3	8.3	6.6
Common arterial trunk	7.9	2.5	3.2
Anomalous pulmonary venous connection	7.2	5.0	3.0
Aortic atresia and mitral atresia or both	6.9	15.1	2.9
Pulmonary atresia with intact septum	7.2	6.4	4.9
Pulmonary atresia with ventricular septal defect	2.4	2.2	
Ventricular septal defect	4.8	2.9	21.9
Atrioventricular septal defect	8.9	5.2	6.4
Double outlet right ventricle	6.2	1.5	4.7
Fallot's tetralogy	2.4	4.5	7.3
Atrial septal defect	—	1.4	4.9
Persistent arterial duct	0.6	—	3.2

*Excluding mitral atresia.

NERICP, New England Regional Infant Cardiac Program.

Analysis of our data by age group (Table 2) produces different results. Atrioventricular septal defect was the most frequent lesion at necropsy (8.9%) and it was also the dominant lesion (15%) in the older age group. Its incidence in the group aged less than one month was low (3%). Nearly all of the 27 cases of atrioventricular defect were associated with major complicating lesions, including severe right ventricular dominance, double outlet right ventricle, and arch hypoplasia; this may account for the high mortality.

The necropsy incidence of arch malformations which impede aortic flow (interrupted arch and arch hypoplasia and coarctation) was 13.8%. Thirteen of the fifteen cases of interruption were less than a month old. Tubular hypoplasia was also more common in the younger group, and eight of the 12 cases with this lesion were less than one month old. Arch lesions themselves are technically amenable to surgical reconstruction but 22 of our 39 cases also had some form of subaortic outflow tract obstruction. The incidence of aortic atresia or mitral atresia or both in the necropsy series was high (9.9%) in those aged <4 weeks. This accords with clinical data which show that 82% of all cases of hypoplastic left heart syndrome present before the end of the first week of life.

The necropsy incidence of pulmonary atresia with intact septum was about 7% in both age groups. The clinical incidence is low (1.9%), both in the first month and overall. Although 60% of all cases present by day 7, the prognosis is poor as shown by the high necropsy incidence. Further investigation demonstrated that 16 of the 21 cases had tiny right ventricular cavities. Right ventricular cavity size and morphology are important,^{13 14} and it was no surprise to find that most of our cases had severe hyper-

trophy of the ventricular wall with almost total obliteration of the apical trabecular and outlet components. These are known to be the cases with the worst surgical prognosis. Also of note was the finding of three cases with grossly dilated right ventricular cavities and thinning of the ventricular myocardium. These were all associated with severe Ebstein's anomaly of the tricuspid valve. Clinically they present with high cardiothoracic index on the chest radiograph. These patients also have a poor prognosis. It is difficult to see from the specimens what potential there is for surgical repair. In our opinion, these cases should be considered as a special subgroup of cases with pulmonary atresia and intact septum.

The incidences of anomalous pulmonary venous connection and of pulmonary atresia with intact septum are similar. Five of the eleven younger cases were known to have had an infradiaphragmatic anomalous connection. Such an anomalous connection was not found in any of the older cases. The early obstruction to the pulmonary venous return at the level of the diaphragm (or through the liver sinusoids when the venous duct closes) almost certainly explains this finding. The overall mortality rate among those cases which present during the first year of life is known to be high.^{15 16} This is in part due to the moribund condition of the child on admission.¹⁷ The poor surgical results reflect this. The success of treatment is dependent on an early diagnosis. Immediate referral to operation after cross sectional echocardiography has recently improved the results, even in cases with infradiaphragmatic connection.¹⁸

Both double outlet right ventricle and complete transposition showed a higher necropsy incidence in the older group (8.6% and 10.0%) than during the

postnatal period (4.0% and 7.3% respectively). Three of the 11 patients with complete transposition who died soon after birth had additional arch hypoplasia. Pulmonary stenosis is well recognised in association with complete transposition, occurring in 15%–33% of all cases.¹⁹ Right ventricular obstruction, however, is less well documented. The observation of additional arch hypoplasia should always suggest the possibility of subaortic stenosis.^{20, 21}

In the necropsy series tetralogy of Fallot and pulmonary atresia with ventricular septal defect were found almost exclusively in the older group. The clinical series shows that 75% of cases do not present until after the age of four weeks. The reasons for this are unclear. The right to left shunt may increase because of pulmonary stenosis or decreasing systemic vascular resistance. Alternatively, it may be because of increasing oxygen demand. Serious cases (13.4%), however, do present within the first week of life. The absence at necropsy of cases aged less than 4 weeks suggests that management of such patients is good. Without doubt, surgical interventions influence the type of case that presents at necropsy. Since we lack the data on the number of cases that come to operation, it is not possible to say whether this is generally successful. Of note is the finding that over 30% of all the necropsy cases had undergone complete repair and a further 20% had palliative procedures. The operation may have hastened death in some cases. Since most of the cases had severe anomalies complicated by additional lesions (Table 3), however, we believe that in these cases operation was attempted on patients whose prognosis was poor from the outset.

Comparison of our data with other series shows a constant emphasis on complete transposition both in the clinical (Table 5) and necropsy (Table 6) series. This is not the case for hypoplastic left heart syndrome (aortic atresia or mitral atresia or both) for which a necropsy incidence of the NERICP series was 15% compared with our value of 7.0%. Nor is it so for interruption of the aortic arch and arch hypoplasia/coarctation. The increased clinical incidence of these has been attributed to the improvements in recognition and referral,⁵ and this would also influence the necropsy incidence. Earlier diagnosis and referral would reduce the number of deaths at local centres and increase the numbers at necropsy at specialised units. There is a noticeable delay in the diagnosis of hypoplastic left heart syndrome in the NERICP series compared with our own.⁵ This, along with the real decrease in incidence at the clinical level, could account for the lower incidence at necropsy seen in our series.

Our incidence of univentricular atrioventricular

connection, in which we have combined hearts with double inlet ventricle with those having the absent connection variant of atrioventricular valve atresia,²² far exceeds that found by others both clinically and at necropsy. This almost certainly relates to differences in classification.²² In this respect, atrial isomerism was not thought of as a physiologically important defect and was, therefore, not given a group of its own. Isomerism is often associated with univentricular atrioventricular connection and under such circumstances would be classified by us as the latter. In the NERICP series hearts with both defects were classified under the heading of heterotaxia. It could be argued that associated lesions are of more haemodynamic importance than the common mixing within the ventricular mass, but the connection to us seems the most striking anatomical finding. None the less, the lack of univentricular atrioventricular connection (or its alternative appellations) in Keith's series¹ must surely be due to the classification of such hearts by their additional lesions.

The criteria used to establish the primary diagnosis in multiple defects are open to differing interpretation and this is one reason for non-uniform categorisation. To ensure that modern comprehensive studies are comparable a detailed classification is needed. Sequential analysis is the first step to comparative studies because anomalies of connections may then be determined without ambiguity. It is insufficient to establish the anatomical cause of death. For this an insight into the spectrum of complicating lesions is also required and hence some degree of subcategorisation is appropriate.

We are indebted to all who have referred their specimens to our collection. We thank staff of the Departments of Pathology and Paediatrics, Brompton Hospital, for their continuing co-operation.

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Subpulmonary pleural effusions in children after cardiac surgery

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SUMMARY Postoperative chest radiographs on 100 children who had undergone cardiac operations were evaluated to determine the frequency of subpulmonary effusions after surgery. Of the 83 patients in whom adequate erect postoperative radiographs were available, 9 (11%) had effusions confirmed by lateral decubitus radiographs. On the frontal chest x ray film, the evidence of an effusion was an increase in distance between the diaphragm and air in the gastric fundus, or an apparent elevation of the right hemidiaphragm. None of the patients examined echocardiographically had associated pericardial effusions. When a subpulmonary effusion was detected diuretic treatment was started or continued. None of the patients had radiographic evidence of residual fluid when they were seen two weeks after their discharge from hospital.

Pleural effusions are common and may be bilateral.¹ When fluid collects in the chest it initially accumulates inferiorly between the lung and the diaphragm and posteriorly in the costophrenic sulcus.² As the amount of fluid increases it spreads around the lung, which retracts towards the hilum. A typical effusion collects mainly laterally and posteriorly, obscures the hemidiaphragm and costophrenic sulcus, and has a smooth concave medial and lateral border.

Occasionally a large volume of fluid may collect between the lung and the diaphragm without obliterating the costophrenic sulcus. These effusions may escape detection on the radiograph unless the degree of suspicion is high.³ They should be suspected if one hemidiaphragm appears to be elevated or if the distance between the left hemidiaphragm and air in the gastric fundus is increased. Subpulmonary effusions have been reported in patients with nephrotic syndrome,^{4,5} metastatic cancer,⁶ congestive cardiac failure, and constrictive pericarditis.²

A missed subpulmonary effusion on the chest radiograph of a child who subsequently died of late tamponade prompted this study to determine the frequency of subpulmonary effusions in children after cardiac operations.

Patients and methods

We studied 100 consecutive children undergoing cardiac operation at this hospital (Table). Their ages ranged from the neonatal period up to 14 years (mean age 3 years 2 months, median age 1 year 6 months).

All children had routine preoperative and supine postoperative radiographs while in the intensive care unit. Most children also had a routine erect chest radiograph on the day of discharge, or before if clinically indicated. Any child thought to have a subpulmonary effusion demonstrated by an increased distance between the gastric air bubble and the lung (Fig. 1a) or an apparent raised right dome of the diaphragm on the erect chest x ray film (Fig. 2) had right or left lateral decubitus radiographs (Fig. 1b) to confirm the presence of an effusion. An echocardiographic examination was performed on all patients with a subpulmonary effusion to detect any associated pericardial fluid. Routine chest radiographs taken two weeks after discharge were also reviewed.

Results

Of the 100 children entered into the study, 10 were transferred to other hospitals and seven died in the intensive care unit without an erect chest radiograph being taken. A subpulmonary effusion was suspected in 17 of the remaining 83 children (13 on the

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Accepted for publication 21 August 1985

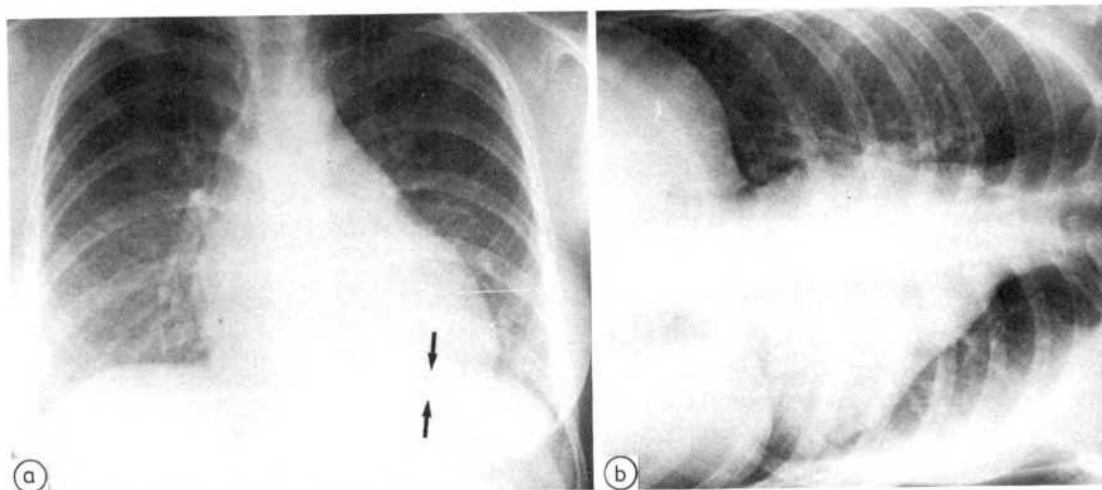


Fig. 1 (a) Erect radiograph showing increased distance between the diaphragm and the gastric air bubble. (b) Left lateral decubitus radiograph of the same patient showing a left sided pleural effusion.

left and four on the right). Effusions were excluded in eight and confirmed in nine children by a lateral decubitus film. All confirmed subpulmonary effusions were present on the left side.

None of the patients with subpulmonary effusions had an associated pericardial effusion detected by cross sectional echocardiography. Three children were not on regular postoperative diuretic treatment when their subpulmonary effusion was noted. There was no radiographic evidence of residual fluid in patients seen two weeks after discharge from hospital.

Discussion

The radiological signs of a subpulmonary effusion are subtle and may be missed.² A subpulmonary

effusion on the left side increases the distance between the air in the gastric fundus and the diaphragm. On the right side the only sign may be a slight elevation of the hemidiaphragm. Occasionally, there is blunting of the lateral costophrenic sulcus (that is loss of the normal acute angle between thoracic cage and diaphragm) and a small lamellar effusion may be seen along the lateral chest wall. When the patient is placed on the side, the fluid is free to move within the chest and collects along the lateral chest wall. Fluid in this position is readily detected by a horizontal ray lateral decubitus radiograph (Fig. 1b). A large effusion may be missed on a frontal radiograph if the above signs are not recognised.

There is some controversy about the origin of subpulmonary effusions. Perhaps the most plausible explanation was put forward by Fleischner.² He

Operation	No	Subpulmonary effusion
Requiring cardiopulmonary bypass:		
Ventricular septal defect	15	3
Tetralogy of Fallot	11	
Mustard operation	7	
Atrial septal defect	5	2
Aortic valvotomy	4	
Atrioventricular canal defect	4	
Anatomical switch for transposition of the great vessels	4	
Fontan procedure	3	1
Mitral valve repair	2	
Rastelli operation	1	
Pulmonary valvotomy	1	
Not requiring cardiopulmonary bypass:		
Coarctation repair	6	
Pulmonary artery band	6	2
Left Blalock operation	5	
Patent ductus arteriosus ligation	5	
Right Blalock operation	4	1

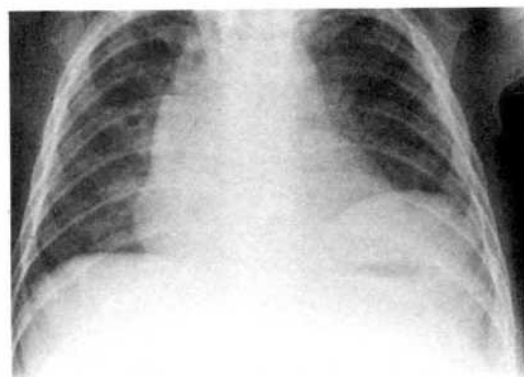


Fig. 2 Erect radiograph showing elevation of the left diaphragm.

stated that recumbency after surgery increases the tendency to lower lobe atelectasis, elevation of the diaphragm, and reduced cough. The lower lobe retracts as soon as a pleural effusion appears. This additional atelectatic pull increases the amount of fluid held between the lower lobe and diaphragm.

In our study 11% of children had a subpulmonary effusion. Their occurrence only on the left side may be explained by the fact that most operations are performed via a central or left thoracotomy incision. In one patient, however, a right thoracotomy for a modified Blalock-Taussig operation produced a left sided subpulmonary effusion. It is of interest that three of the nine children with effusions were not receiving diuretics, which we usually prescribe after cardiac surgery.

In conclusion, we found an unexpectedly high number of subpulmonary effusions after cardiac surgery in children. Diagnosis may be suspected after careful examination of an erect chest radio-

graph and can be confirmed by examination of a chest radiograph taken from the appropriate lateral decubitus view. This high frequency of effusion confirms the need for routine postoperative diuretics after cardiac surgery.

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The heart and tuberous sclerosis

An echocardiographic and electrocardiographic study

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SUMMARY Cross sectional echocardiography, 12 lead electrocardiography, and 24 hour ambulatory electrocardiography were performed in eleven patients with tuberous sclerosis. Echocardiography showed single or multiple intramyocardial masses, most commonly in the ventricular septum, suggestive of rhabdomyomata in seven of the eleven cases. One patient with a normal echocardiogram showed ventricular pre-excitation on electrocardiography, with tachycardias of 180 beats per minute on ambulatory monitoring. Sinus bradycardia, sinus tachycardia, and supraventricular tachycardia were also seen, but their importance is uncertain.

Echocardiography and electrocardiography should be routinely performed in the assessment of patients with tuberous sclerosis and ambulatory electrocardiography should be considered in those with seizures that respond poorly to anticonvulsants.

Since the first reported case of cardiac rhabdomyoma in 1862¹ the association of this tumour with tuberous sclerosis has become well recognised. Most information on these tumours has of necessity been related to morbid anatomy and there is little information on the frequency of cardiac involvement in such patients during life. With the advent of echocardiography, non-invasive antemortem diagnosis of intracardiac masses has become possible,² and ventricular rhabdomyomata have been detected with both M mode³ and cross sectional^{4,5} echocardiography.

Syncope, seizures, and "funny turns" occurring in patients with tuberous sclerosis are likely to be attributed to cerebral causes. These patients, however, may have abnormal hearts and such symptoms may be of cardiac origin. I have assessed the frequency of echocardiographic abnormalities in patients with tuberous sclerosis and have investigated whether the presence of cardiac tumours in these patients was related to detectable disturbances in cardiac rhythm.

Patients and methods

A standard letter was circulated to neurologists and paediatricians within the paediatric cardiology catchment area of this hospital (population approximately five million), asking for permission to write to any patients with tuberous sclerosis under their care. Letters were also sent to patients registered with the Tuberous Sclerosis Association and living within the same catchment area inviting them to join the study. Twenty three patients with tuberous sclerosis were identified; 11 of them agree to participate in the study. One case had already been investigated at this hospital because of palpitation.

The patients were aged from 4 to 54 years (mean (SD) 20(13)). Nine patients had mental retardation ranging from mild educational subnormality to severe retardation with pronounced hyperactivity. The two mentally normal adult patients had adenoma sebaceum and subungual fibromata as the only clinical manifestations of tuberous sclerosis. Eight of the eleven patients had some form of epilepsy and were taking diazepam, clonazepam, phenytoin, sodium valproate, carbamazepine, or a combination of these anticonvulsants. All subjects were examined by cross sectional echocardiography, 12 lead electrocardiography, and 24 hour ambulatory electrocardiography. With the exception of the one case already under the care of this hospital none of the

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Accepted for publication 2 September 1985

patients had previously undergone cardiac investigation.

Results

ECHOCARDIOGRAPHY

Seven of the eleven patients had abnormal echocardiograms (Figure). Single or multiple echodense masses were detected in the ventricular septum alone in four cases, in the septum and posterior left ventricular wall in one, and in the posterior left ventricular wall alone in two. The masses ranged in diameter from 0.3 cm to 1.2 cm. All seven patients with abnormalities on the echocardiogram were epileptic and all were at least slightly mentally retarded. No masses affecting the atria were detected, and apart from the intramyocardial masses the cardiac anatomy appeared normal.

ELECTROCARDIOGRAPHY

Four patients had unremarkable ambulatory electrocardiographic recordings. In the seven remaining

cases sinus tachycardias at rates of approximately 150 beats per minute, unrelated to seizures, occurred in two patients aged 21 and 23 years, both of whom were severely mentally retarded and bed-ridden. These patients also showed abrupt slowing of sinus rhythm from 70 to 47 and from 100 to 60 beats per minute respectively while awake but at rest. Both had involuntary movements and frequent episodes of hyperactivity, were taking anti-convulsants, and had abnormal echocardiograms. Sinus tachycardias of 150 beats per minute occurred in two other patients during seizures. Abrupt sinus slowing was seen in one further subject, a 35 year old woman whose heart rate abruptly fell from 70 beats per minute to 45 beats per minute while she was awake but at rest; a pronounced sinus arrhythmia was seen on the 12 lead electrocardiogram. She was taking no medication and had a normal echocardiogram. Two patients, one aged 14 who had an abnormal echocardiogram and one aged 4 years who had a normal echocardiogram, had supraventricular tachycardias at rates of 140 and 180 beats per minute

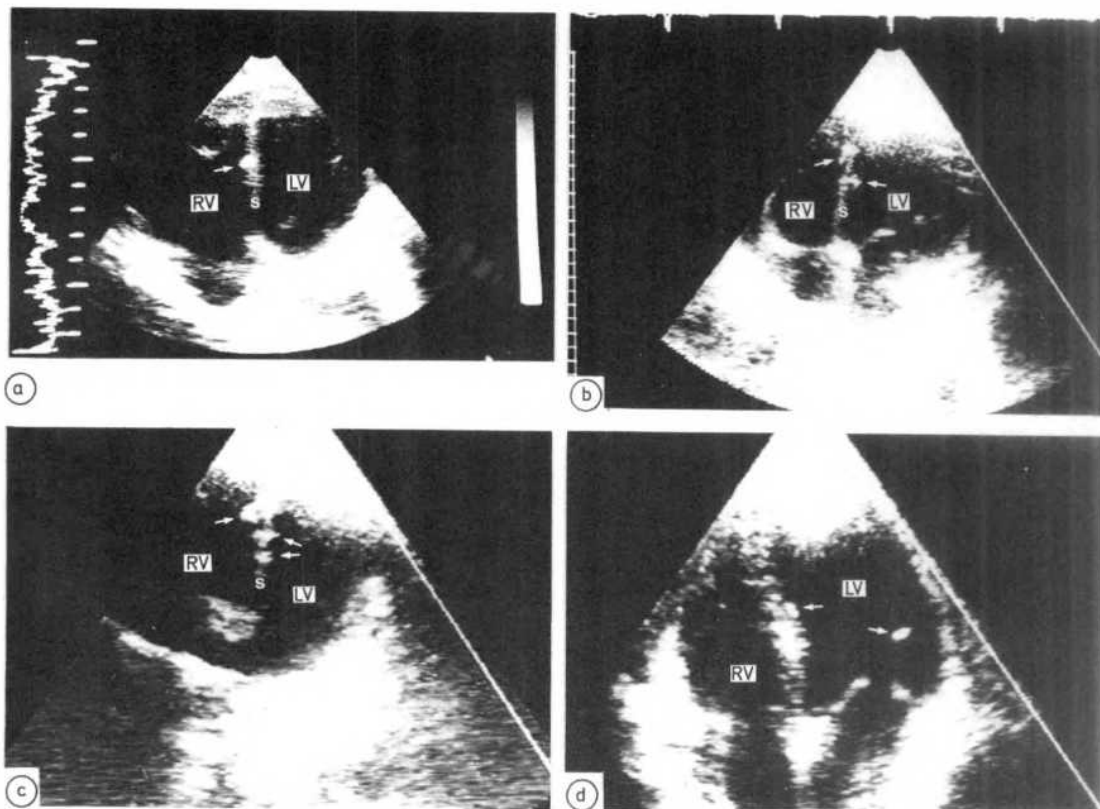


Figure Examples of echocardiographic abnormalities in patients with tuberous sclerosis. Intramyocardial masses (arrowed) were detected as single (a) or multiple (b, c) lesions in the ventricular septum and were also seen in the posterior left ventricular wall (d). RV, right ventricle; LV, left ventricle; S, ventricular septum.

respectively that occurred during seizures and rapidly reverted to sinus rhythm after the seizures. In the latter case, ventricular pre-excitation (with a PR interval of 50 ms and without a delta wave) was present throughout the 24 hour recording period and 12 lead electrocardiogram. Both patients were regularly taking anticonvulsants. Sinus bradycardia at rates of between 60 and 45 beats per minute was present throughout the ambulatory recording of one 14 year old boy with an abnormal echocardiogram whose seizures were treated with diazepam alone.

Discussion

STUDY POPULATION

The prevalence of tuberous sclerosis in Oxford has been estimated at between 1:15 000 and 1:30 000.⁶ In my study 23 cases were detected in a population of approximately five million (approximately 1:217 000). The method of identifying those with tuberous sclerosis was relatively crude and there can be little doubt that a considerable number of cases were not identified. Patients with mild manifestations of disease are less likely to seek medical attention, and the patients with tuberous sclerosis in this paper are likely to be those who are more severely affected.

ECHOCARDIOGRAPHY

The high frequency of rhabdomyoma of the heart in patients dying of tuberous sclerosis was first suggested by Steinbiss, who found clinically unsuspected tumours at necropsy in all six patients with tuberous sclerosis encountered over a ten year period.⁷ This association was confirmed by Crome, who also reported two cases of congenital fibroelastosis of the heart in a necropsy study of tuberous sclerosis.⁸

The present study detected intramyocardial masses in seven (64%) of 11 patients. In no case did there appear to be any interference of cardiac function due to a mass effect alone. Echocardiographic abnormalities suggestive of rhabdomyoma are detectable in a large proportion of patients with tuberous sclerosis, particularly when the clinical manifestations of the disease are pronounced.

ELECTROCARDIOGRAPHY

The possibility that cardiac tumours may interfere with normal conduction pathways was first suggested by Wegman and Egbert, who reported multiple rhabdomyoma nodules invading the conducting system in a girl who had tachycardia with rates up to 200 beat per minute.⁹ Duras reported a further case in which frequent extrasystoles were noted in a patient with severe mental retardation and adenoma

sebaceum.¹⁰ A case presenting with palpitation has been described,¹¹ in which the patient had classic stigmata of tuberous sclerosis. Electrocardiography showed the symptoms to be due to multifocal ventricular extrasystoles; an intraventricular conduction defect was also noted. Ventricular septal rhabdomyoma may also be associated with neonatal complete heart block.^{12 13} Rhabdomyomatosis may be the underlying cause of ventricular pre-excitation, with rhabdomyomatous fibres forming an accessory atrioventricular pathway and leading to symptomatic tachycardias.¹⁴ The only patient in the present series who showed ventricular pre-excitation had an apparently normal echocardiogram, but the resolution of ultrasonic imaging may be incapable of detecting masses that are much smaller than 3 mm in diameter. Indeed, in the case report referred to above,¹⁴ the rhabdomyomatous changes were extensive microscopically but only appeared macroscopically as a localised thickening of the mitral valve and may well have been missed by echocardiography.

Information on the terminal events in patients with tuberous sclerosis suggests that status epilepticus, renal failure,¹⁵ and intercurrent infection¹⁶ are the principal causes of death. Multiple large cardiac tumours may cause heart failure and death due to a mass effect alone,¹⁷ but the frequency and clinical importance of cardiac arrhythmias have yet to be fully evaluated. Apart from the one patient in this series with ventricular pre-excitation and tachycardias, the importance of the ambulatory electrocardiographic findings is uncertain. Most of the patients were taking anticonvulsant drugs, and since these may produce bradycardia it may be particularly difficult to determine whether cardiac arrhythmias in epileptic patients precede or follow the onset of seizures. Even in healthy teenage boys ambulatory electrocardiography may show alarming features such as sinus bradycardia, sinus arrest, five to one atrioventricular block, supraventricular tachycardia at rates up to 200 beats per minute, and short episodes of ventricular tachycardia.¹⁸ For this reason, 24 hour electrocardiographic recordings are best reserved for the cases of tuberous sclerosis in which seizure control deteriorates despite anticonvulsant treatment or in which a cardiac cause of syncope is suspected on other grounds.

This study has shown that intramyocardial masses detectable by echocardiography are found in a high proportion of patients with tuberous sclerosis, confirming a recent report from the United States.¹⁹ While the findings of ambulatory electrocardiography in epileptic patients are difficult to interpret, it is clear that potentially serious arrhythmias may occur. Echocardiography and 12 lead elec-

trocardiography should be routinely performed in patients with tuberous sclerosis, and in cases in which seizures are difficult to control the possibility of a cardiac rather than a cerebral aetiology should be borne in mind.

I thank Mrs Ann Hunt of the Tuberous Sclerosis Association for her administrative help; Dr Leon Gerlis and Dr Gordon Williams for their advice and encouragement; Mrs Gill Wharton for her technical assistance; and Dr D F Dickinson, Killingbeck Hospital, Leeds; Dr R N Hakin, St Luke's Hospital, Bradford; Dr D W Sumner, St James Hospital, Leeds; Dr G M Wilson, Staincliffe General Hospital, Dewsbury; and Dr E G S Spokes, Bootham Park Hospital, York, for their cooperation.

JLG is supported by the National Heart Research Fund.

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Case reports

Atrioventricular and sinoatrial block in thyrotoxic crisis

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SUMMARY A 55 year old woman in thyrotoxic crisis developed atrial fibrillation, atrioventricular block, and sinoatrial block in rapid succession. All of these abnormalities resolved completely after antithyroid treatment. This course of events illustrates the profound effect of thyroid hormones on cardiac function. In view of the potential aggravation of atrioventricular conduction disturbance by beta adrenergic blocking agents, thyrotoxic patients should be carefully screened for electrocardiographic evidence of conduction disturbance before the administration of such drugs.

Hyperthyroidism is commonly associated with sinus tachycardia and atrial fibrillation. A less well known complication of thyrotoxicosis is impaired atrioventricular conduction. Complete atrioventricular block complicating hyperthyroidism has generally been described in patients with additional risk factors such as infection, drugs, or electrolyte imbalance.¹⁻⁶ In a few, however, thyrotoxicosis was the only cause of atrioventricular block.^{4,5} We describe a patient with thyrotoxic crisis in whom atrial fibrillation, atrioventricular block, and sinoatrial block developed in rapid succession. All of these abnormalities resolved after antithyroid therapy.

Case report

A 55 year old Arab woman was admitted to this hospital in August 1983 because of progressive weakness, dyspnoea, diarrhoea, and a weight loss of about 10 kg in recent months. Hyperthyroidism had been diagnosed two years before and she had been treated with propylthiouracil and digoxin, but these drugs had been stopped a month before admission.

On examination she was pale, tense, and moderately dyspnoeic. Blood pressure was 170/70 mm

Hg and her pulse was regular (100 beats/min). There was bilateral lid lag and impaired convergence. The thyroid gland was diffusely enlarged with an audible bruit. Her skin was warm and moist, and she had a fine tremor of the hands. There was a loud first heart sound and a 3/6 systolic murmur over the heart apex and the pulmonary area.

Laboratory examinations showed a haemoglobin concentration of 9.5 g/dl, white blood cell count of 4900/mm³, and sedimentation rate of 36 mm/h. Triiodothyronine resin uptake was 48% (normal 25-45) and serum thyroxine concentration was 30 µg/dl (normal 4.5-11.5 µg/dl) (386 nmol/l, normal 58-148 nmol/l). The concentration of serum thyroid stimulating hormone was 2.0 µU/ml (normal 10 µU/ml). There were no antithyroid antibodies. Routine blood biochemical analysis including serum calcium was normal, apart from a serum alkaline phosphatase concentration of 170 IU/l (normal 40-80 IU/l). The electrocardiogram on admission was normal with a sinus rhythm of 100 beats per minute and a PR interval of 0.16 s. An x ray film of the chest showed moderate bilateral congestion of pulmonary vessels. An echocardiographic study showed asymmetric hypertrophy of the septum. She was started on daily doses of propylthiouracil (600 mg) together with digoxin (0.25 mg) and frusemide (40 mg). One day later a transient episode of atrial fibrillation was recorded.

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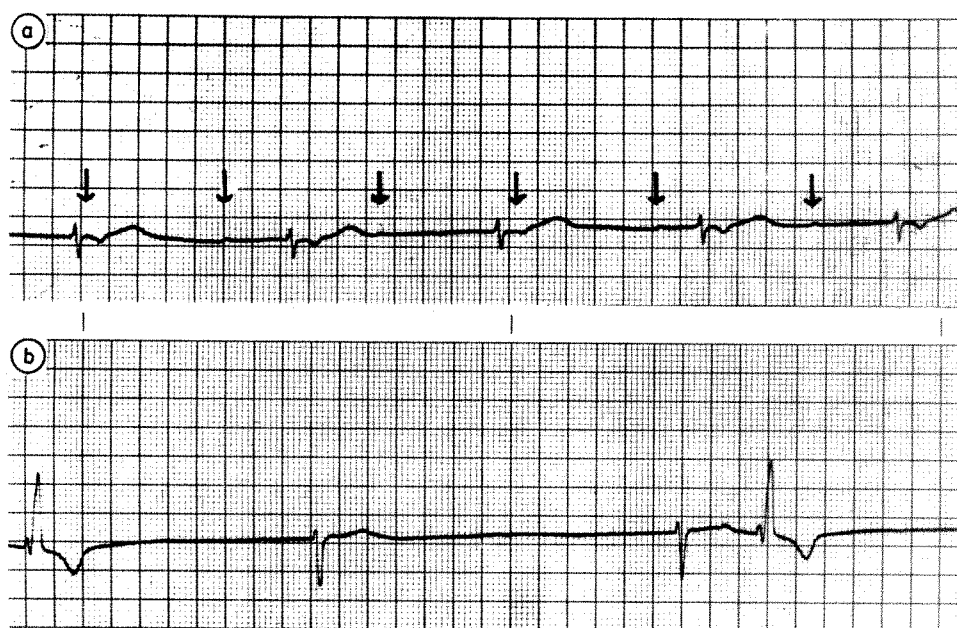


Figure Electrocardiograms in a patient in thyrotoxic crisis showing (a) complete atrioventricular dissociation (arrows indicate P waves) and (b) sinoatrial block with ventricular escape.

After three days in hospital the patient's diarrhoea increased and her temperature rose to 38°C. On the same day, after a single oral dose of propranolol (10 mg) there was an episode of syncope. A repeat electrocardiogram after syncope showed complete atrioventricular dissociation with an atrial rate of 66 beats per minute and ventricular rate of 23 beats per minute (Fig. a). After treatment with atropine and isoprenaline and withdrawal of propranolol, atrial fibrillation developed and this was followed by the resumption of sinus rhythm. Although sinus rhythm was largely maintained thereafter, several short episodes of sinoatrial block with ventricular escape were recorded (Fig. b). In the following days huge inverted T waves appeared in the anterior chest leads without ischaemic chest pains and without raised concentrations of serum enzymes.

She continued to have a high temperature. All blood and stool cultures were negative. Severe left heart failure and stupor developed. The daily dose of propylthiouracil was increased to 1 g and a larger dose of diuretic was given. These measures were followed by gradual improvement with a return to normal body temperature and bowel movements. Three weeks after admission she was given 8 mCi of iodine-131. Two months later her serum thyroxine had fallen to 14 µg (180 nmol/l), the tri-iodothyronine resin uptake was 30%, and the

electrocardiogram was normal. She is in good health 18 months later and requires no drug treatment.

Discussion

Although abnormal atrioventricular conduction has been reported in some patients with thyrotoxicosis,¹⁻⁶ this abnormality is not generally acknowledged to be a complication of hyperthyroidism, which is more commonly associated with sinus tachycardia and atrial fibrillation.⁷⁻⁹ Complete heart block associated with thyrotoxicosis has generally been seen in patients with additional risk factors such as infectious diseases,³ rheumatic fever,¹ hypercalcaemia,⁶ or digitalis treatment. In such patients, complete heart block might have been the result of a primary insult aggravated by the presence of thyrotoxicosis. In other patients, however, thyrotoxicosis has been the only underlying disease, and control of thyroid disease has restored normal atrioventricular conduction.^{4,5} In our patient no risk factor other than hyperthyroidism was identified and all cardiac problems were resolved after anti-thyroid therapy. It should be noted, however, that atrioventricular dissociation was first observed after a small (10 mg) dose of propranolol and a possible role for this drug in precipitating the conduction disturbance cannot be excluded.

Episodes of sinoatrial block are a unique and hitherto unrecorded feature of the electrocardiographic abnormalities observed during a thyrotoxic crisis. The coexistence of atrial fibrillation, atrioventricular block, and sinoatrial block, which were seen in rapid succession in our patient, illustrates the profound effect of thyroid hormones on cardiac function. Prolongation of the P-R interval is seen in 5% of hyperthyroid patients.¹⁰ Because beta adrenergic blocking agents could aggravate an atrioventricular conduction disturbance, thyrotoxic patients should be carefully screened for electrocardiographic evidence of conduction disturbances before and during the administration of such drugs.

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Myocardial tuberculoma with rupture and pseudoaneurysm formation—successful surgical treatment

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SUMMARY A case of left ventricular pseudoaneurysm due to rupture of a myocardial tuberculoma is presented. The diagnosis of pseudoaneurysm was initially suggested by echocardiography and was confirmed by angiocardiography. The aetiology was suggested at operation and confirmed by histological examination. This is a very rare condition which is usually diagnosed only at necropsy.

Case report

A 38 year old African hospital employee had a severe, central, crushing chest pain which lasted for four hours. For the next five days he had intermittent pleuropericardial type pain in the left side of the chest. He then sought medical advice. He gave no history of chest pain before this. Five years ago he had had fever associated with patchy bronchopneumonic infiltration of the right lung base; sputum analysis and culture were negative for pathogens. Two months after that he had transient atrial fibrillation which spontaneously reverted to sinus rhythm. A tuberculin skin test had been positive in 1976. The patient had never had treatment for tuberculosis.

Physical examination at the time of admission showed a healthy looking adult in no acute distress. Pulse rate was 80 beats per minute and regular, temperature was 37°C, and blood pressure was 140/100 mm Hg. Jugular venous pressure was not raised; there was no cardiac enlargement; first and second heart sounds were normal. There was no pericardial rub. The chest was clear; the liver and spleen were not palpable and there was no oedema in the legs.

The electrocardiogram showed changes of an inferior myocardial infarction. An electrocardiogram recorded three years earlier had been normal. The chest x ray film showed a heart of normal size with clear lung fields. Serum concentrations of cardiac enzymes were normal and the erythrocyte sedimentation rate was 35 mm/hour (normal 0-5). The cross sectional echocardiogram in the long axis parasternal view showed a pouch posterior to the left ventricle

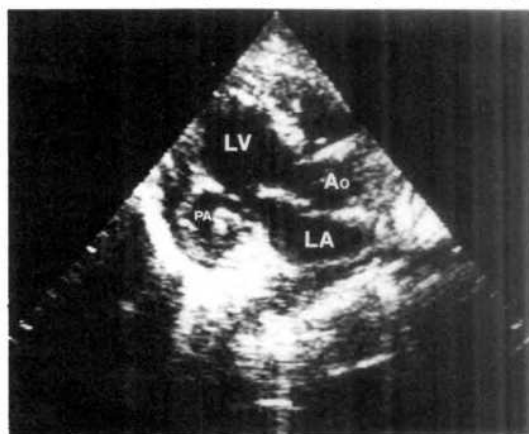


Fig. 1 Cross sectional echocardiogram in parasternal long axis view showing the pseudoaneurysm communicating by a narrow neck with the left ventricular cavity just below the mitral valve. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pseudoaneurysm.

communicating with the left ventricular cavity through a narrow necked channel (Fig. 1). M mode echocardiography showed a large echo free space posterior to the left ventricular epicardium. These findings suggested a pseudoaneurysm in the left ventricle. Coronary angiography showed normal left and right coronary systems; left ventricular angiography demonstrated a multi-loculated pseudoaneurysm (Fig. 2).

Four weeks later the patient underwent surgery. The posterior pericardium was found to be thickened and there was a haemorrhagic pericardial effusion. A hole, 1 cm in diameter, was found in the lower left ventricular wall. The hole was patched and the pericardium and pseudoaneurysm were resected and sent for histological examination. The

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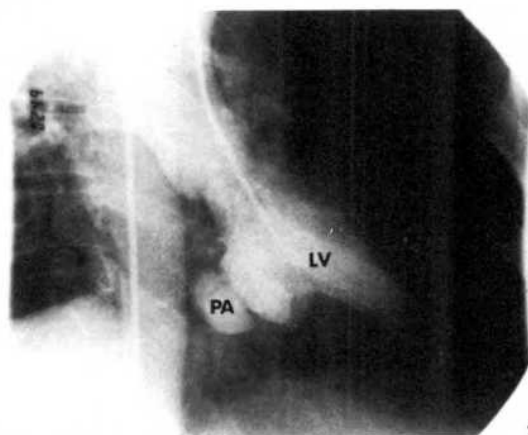


Fig. 2 Left ventricular angiogram showing contrast material filling a pseudoaneurysm on the inferior surface of the left ventricle (right anterior oblique projection). LV, left ventricle; PA, pseudoaneurysm.

early and late postoperative periods were without complications.

Histopathological examination showed that the pseudoaneurysm lining was a mixture of myocardium and pericardium. There was extensive fibrosis and a large number of granulomas with areas of central caseation surrounded by epithelioid cells and multinucleated giant cells. Although no acid fast bacilli were seen and culture remained sterile, the presumptive diagnosis was tuberculoma of the myocardium with rupture and pseudoaneurysm formation. The patient was treated with isoniazid, rifampicin, and ethambutol. In the next two months his weight increased by 8 kg and he remains symptom free 10 months after operation.

Discussion

Tuberculosis of the myocardium was rare even in the early 1900s and it is becoming more rare with improved medical treatment. Custer and Charr reviewed more than 14 000 deaths due to tuberculosis and found only 64 cases (0.44%) of tuberculosis of the heart.¹ Three types of myocardial involvement are described²: localised mass (tuberculoma), diffuse myocarditis, and miliary lesions. The mechanisms of myocardial involvement are direct retrograde spread from mediastinal lymph nodes, extension from a pericardial focus, and blood dissemination. There are few reported cases of myocardial tuberculoma, and all were diagnosed at necropsy.³⁻¹² Reported presentations include complete heart block,^{6,9} right ventricular outflow obstruction,¹⁰ aortic regurgitation,¹¹ superior vena cava obstruction,³ or left ventricular aneurysm.¹² Our

patient appears to be the first case of myocardial tuberculoma with rupture and pseudoaneurysm formation which has been treated successfully.

The diagnosis of pseudoaneurysm was suspected from the echocardiogram which had features similar to those described by Katz *et al*,¹³ Roelandt *et al*,¹⁴ and Sears *et al*,¹⁵ except that the pseudoaneurysm wall was more thickened in our patient, probably due to the inflammatory aetiology. The diagnosis was confirmed by angiography; the aetiology was demonstrated histologically. Although no acid fast bacilli were seen or grown, tuberculosis is the most likely diagnosis. Sarcoidosis can produce a similar picture with localised aneurysm¹⁶ but this entity is very rare in Saudi Arabia whereas tuberculosis is common. A tuberculous aetiology is further supported by the histological demonstration of central caseation, and the patient's clinical improvement after surgery and antituberculous therapy.

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Efficacy of an implanted automatic defibrillator which had induced atrial fibrillation

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SUMMARY A 54 year old man with refractory life threatening ventricular tachycardia was given an automatic defibrillator. The initial system was a transvenous defibrillator coil electrode and this was later modified by implantation of two patch electrodes at thoracotomy.

The modified system successfully controlled ventricular tachycardia. On one occasion reversion of ventricular tachycardia by the defibrillator precipitated atrial fibrillation, a previously unreported side effect.

Internal defibrillators have been introduced to treat refractory and repeated ventricular tachycardia or fibrillation. We describe a patient in whom cardiac arrest was caused by ventricular fibrillation. A defibrillator was implanted four years after myocardial infarction.

Case report

In 1979, when he was 50, this man had had an inferoposterior myocardial infarction which was complicated with late ventricular tachycardia and cerebral embolism. Treatment with disopyramide was started and this was later changed to amiodarone (400 mg/day) on the basis of Holter tape recordings which consistently showed frequent ventricular extrasystoles and couplets. He did not have angina pectoris or signs of left ventricular heart failure.

On 17 September 1983 he suddenly collapsed and cardiopulmonary resuscitation was carried out by bystanders. When the rescue team arrived ventricular fibrillation was detected and defibrillation was performed with 300 J.

At examination blood pressure was 160/110 mm Hg. A pansystolic murmur of grade II/VI intensity was recorded in the fourth intercostal space at the left sternal border. This had been present before the cardiac arrest. An electrocardiogram showed prominent depression of the J point with a horizontal ST segment in the precordial leads. The electrocardiogram subsequently showed sinus rhythm of 72 beats per minute with an axis in the frontal plane of

-10°, QRS width of 0.10 s, Q wave in lead III, and QR duration of 0.38 s.

Serum electrolytes and creatinine and blood glucose concentrations were within the normal range. Serum aspartate aminotransferase activity was 113 IU/l (normal 11-33 IU/l), lactic dehydrogenase was 425 IU/l (normal 200-400 IU/l), and creatine kinase was 51 IU/l (normal 0-150 IU/l) immediately after admission. Serum creatine kinase concentration reached a peak (268 IU/l) eight hours after admission but the MB fraction remained below 9 IU/l. A chest x ray film showed cardiomegaly with bilateral pulmonary venous congestion.

A coronary angiogram showed a proximal occlusion of the right coronary artery. An occlusion of the middle part of the circumflex artery was bridged by an extensive collateral circulation and there was a mild stenosis of the first diagonal artery of the left anterior descending artery. The inferior wall was akinetic. A left ventricular angiogram did not show any septal defect or mitral regurgitation. Ejection fraction, as measured with radionuclides was 42%. Four weeks later a basic electrophysiological study was performed. Stimuli were delivered by a Jansen stimulator at a constant current of <1 mA with pulse width of 2 ms. Stimulation was applied above the right ventricular apex. Sustained hypotensive ventricular tachycardia with a cycle length of 240 ms was produced when double stimuli were applied to the heart in sinus rhythm. Rhythm was easily reproduced with double stimuli on a ventricular driven rhythm of 110 beats per minute.

In the subsequent serial drug testing procedure, intravenous procainamide on its own (16 µg/ml and 6.5 µg/ml) was ineffective in preventing stimulated

tachycardia and it was still possible to induce ventricular tachycardia or fibrillation with the original stimulation protocol when the patient was on beta blockers or tocainide. After three weeks loading with oral amiodarone, ventricular fibrillation could still be easily induced by double stimuli on a paced rhythm of 90 beats per minute, and this situation was unchanged when amiodarone was given in combination with oral mexiletine. When amiodarone was given in combination with procainamide induction of fibrillation was slightly more difficult and double stimuli given on a basic rhythm of 110 beats per minute produced a hypotensive ventricular tachycardia of 150 beats per minute. Hence, the patient was started on oral procainamide (1.5 g three times a day) in combination with amiodarone (600 mg). This regimen was not considered to be effective because Holter tracings showed multiform ventricular premature beats and the patient had gastrointestinal symptoms and a productive cough.

On 11 April 1984 an automatic implantable defibrillator (AID-B^R) (Intec Systems, Pittsburgh, USA) was implanted under general anaesthesia. A bipolar electrode was passed through the left cephalic vein and placed in the right ventricular apex. The amplitude of the R wave was 12 mV. The Seldinger technique was used to place a classic defibrillator coil in the superior caval vein and a subxiphoid incision

was made preparatory to positioning of a defibrillation patch.

Ventricular tachycardia with a cycle length of 320 ms could be induced with programmed electrical stimulation and could be stopped repeatedly with 5 J delivered through an external device (Fig. 1). In an attempt to induce ventricular fibrillation with programmed stimulation, however, ventricular tachycardia was induced by a burst of stimulation and when 20 J was delivered by the external cardioverter-defibrillator through the coil and patch the tachycardia rate was increased. A further shock of 30 J stopped the tachycardia. External cardioversion was needed to terminate ventricular fibrillation.

Anterolateral left thoracotomy was carried out so that a large defibrillation patch and a small defibrillation patch could be positioned in the pericardial space. The defibrillation threshold for ventricular fibrillation was <20 J. With the impulse generator in the abdominal pouch, fibrillation was produced by application of an alternating current. After a charge time of 8.2 s, a first shock of 25.5 J was given after another 14 seconds. A third shock was needed to convert the ventricular fibrillation to sinus rhythm.

While the patient was still in hospital, an episode of ventricular tachycardia with loss of consciousness

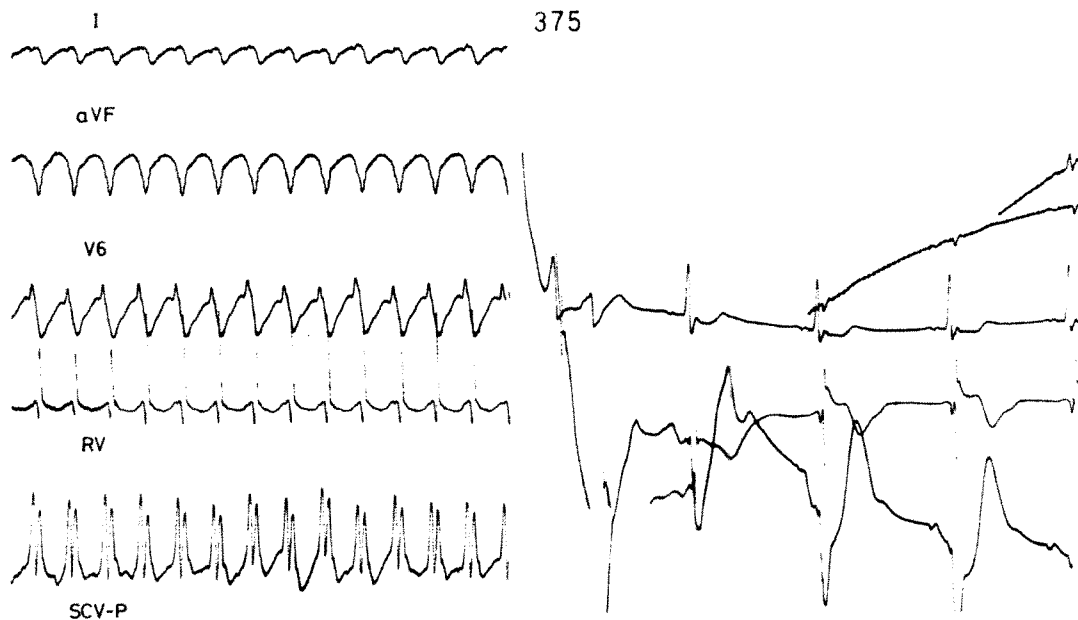


Fig. 1 Efficacy of defibrillator during monomorphic ventricular tachycardia. At implantation monomorphic tachycardia (cycle length 340 ms) was interrupted by a 5 J shock between a coil in the superior caval vein and a patch in the pericardial space (SCV-P). Ventricular fibrillation, however, was not terminated by 35 J shock. RV, bipolar electrode in right ventricle. Paper speed was 25 mm/s.

was terminated by the first shock. Termination of a recurrence required two internal shocks.

The patient was discharged in excellent condition, without antiarrhythmic drugs. Because we feared that the threshold of the defibrillator for ventricular fibrillation might be too high, a control electrophysiological study was performed on 25 May. Ventricular monomorphous tachycardia with cycle length of 330 ms was induced by double stimuli on a basic paced rhythm of 110 beats per minute. It was instantaneously detected and corrected by the first shock.

When a second episode of ventricular tachycardia terminated spontaneously a shock was given 290 ms after the P wave, and this produced long lasting atrial fibrillation and a ventricular rate of 100 beats per minute (Fig. 2). Ventricular fibrillation was produced by application of alternating current (50 Hz) for 2 s and the first shock of 25.5 J converted both rhythms to sinus rhythm. The patient was discharged after 24 hours. He is back at work.

Discussion

Ventricular fibrillation causes most sudden deaths from heart disease.¹ The speed with which ventricular fibrillation can be terminated by defibrillation seems to be an important factor in determining the success of cardiopulmonary resuscitation,² and an automatic implantable device that detects and corrects ventricular fibrillation immediately will be of considerable benefit in high risk patients. Such a

device has been developed and implanted in more than 250 patients.³⁻⁵

The clinical results are good, with a 25% decline in mortality at one year.⁵ These results were obtained in patients with older units and before the use of two patches or larger patches had been considered.^{3,4} The 12 month survival rate in patients fitted with defibrillators is reported to be as high as 97.2% from ventricular tachycardia or fibrillation; it is 83.4% from all types of cardiovascular disease. These results show that implantable defibrillators are better than other forms of treatment for refractory ventricular rhythm disturbances.⁵

Much research has been done on the ideal positioning and size of the paddles and on the amount and character of the energy delivered to the myocardium.⁶ These studies led to the concept of a defibrillation threshold—that is the application of an appropriate amount of energy to the myocardium for a critical time.⁶ The sensing and defibrillation thresholds must be adjusted during implantation of the device. This influences the surgical technique and is relevant to previous and intended operations.⁷ If no other cardiovascular surgery is performed at the time of implantation, it is possible to insert the apical electrode through a small subxiphoid incision, as was our intention.⁸ This case report, however, confirms that some patients may show a high defibrillation threshold during the operation, or may even go into ventricular fibrillation when defibrillatory shocks are given. The conversion rate with the original spring patch defibrillator for mono-

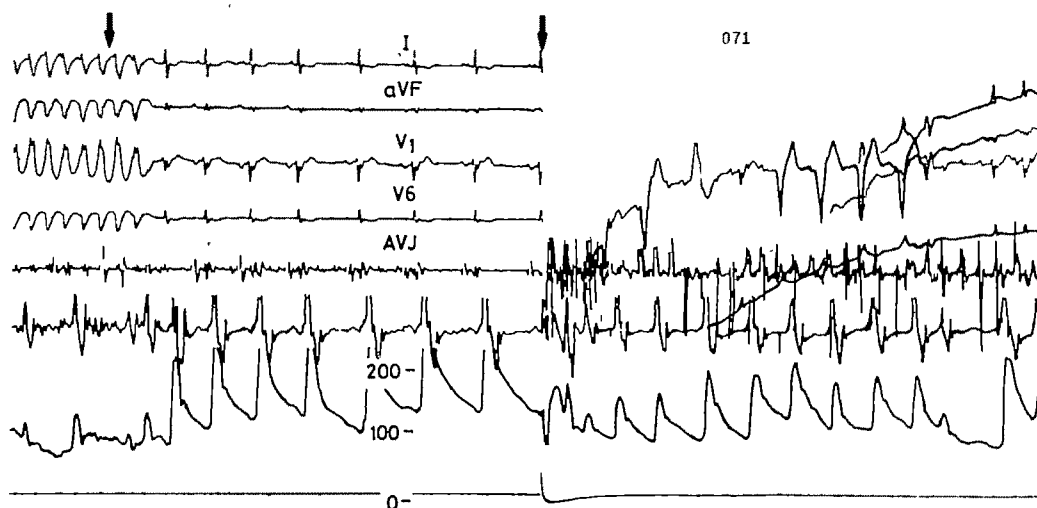


Fig. 2 Electrophysiological study after implantation of defibrillator. The induced regular ventricular tachycardia terminated spontaneously but was sensed (arrow at point of detection) by the defibrillator before sinus rhythm returned. An internal shock given 290 ms after the P wave resulted in atrial fibrillation, as shown by the deviation of the atrioventricular junction (AVJ) electrocardiogram. Lower tracing shows aortic pressure (mm Hg). Paper speed was 25 mm/s.

morphous ventricular tachycardia is 77–86%, but the conversion rate is higher for polymorphous ventricular tachycardia and fibrillation when the size of the shock delivered to the myocardium is increased.⁷ About 10% of patients require two patches to produce a sufficiently low energy threshold.⁷ In these cases access through a subxiphoid incision is not adequate. Treatment of our patient with amiodarone may explain his high defibrillation threshold at operation.⁹

Acceleration of ventricular tachycardia with occurrence of fibrillation is a potential risk of all cardioversion systems, but this effect is less frequent with these devices than with burst pacing.¹⁰ Our case report shows that currently available defibrillators are capable of delivering a rescue shock because they can generate up to three more shocks after the initial shock.³

Control studies should be performed after implantation when it has not been possible to establish the efficacy or the correct sensing of clinical or induced arrhythmias during the implantation of the defibrillator, or when doubts about efficacy remain. We proposed a control study to our patient because cardioversion of ventricular fibrillation during implantation required three shocks, and two consecutive shocks were needed to convert clinical ventricular tachycardia to sinus rhythm. He might have required a high energy device. During the electrophysiological study correct sensing of both ventricular tachycardia and ventricular fibrillation were proved while the patient was under short general anaesthesia. We also found that when the device's capacitors were charged and the arrhythmia stopped spontaneously a shock was given when sinus rhythm returned. Synchronous shocks given during sinus tachycardia, supraventricular tachycardia, or atrial fibrillation are not known to have caused ventricular tachycardia or fibrillation.³ In our patient such a shock caused atrial fibrillation. It is clear, however, that because of synchronisation to ventricular rhythm during tachycardia the shock will often be dissociated from the atrial activity so that short lasting atrial arrhythmias may occur.³ The device has not been developed to treat atrial flutter or

fibrillation, but these rhythm disturbances may trigger the defibrillator, and there is reversion to sinus rhythm in 50% of such episodes.¹¹

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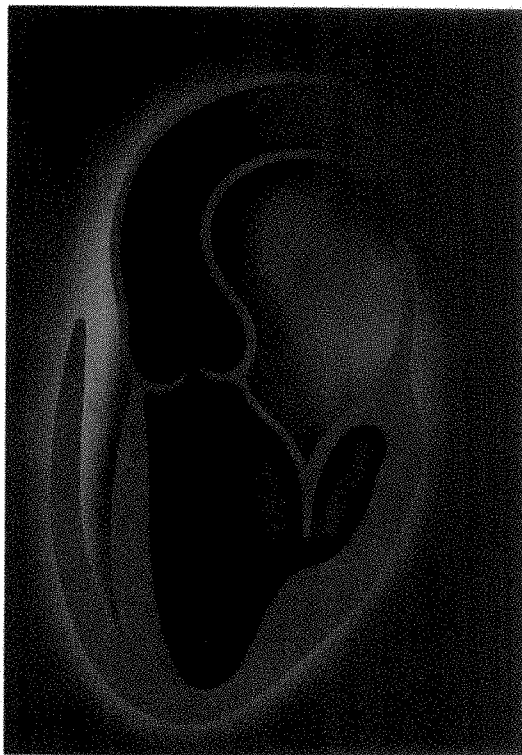
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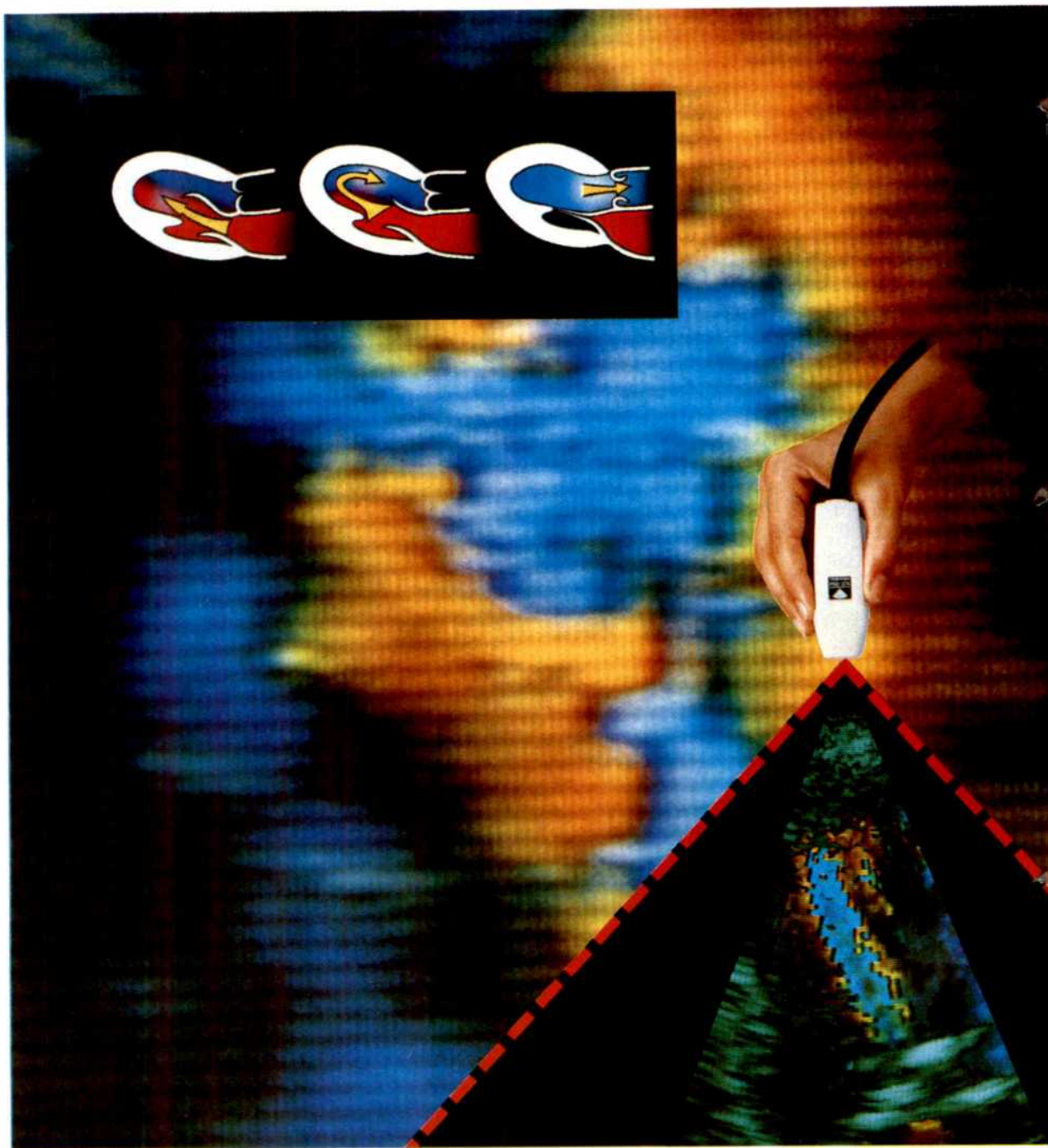


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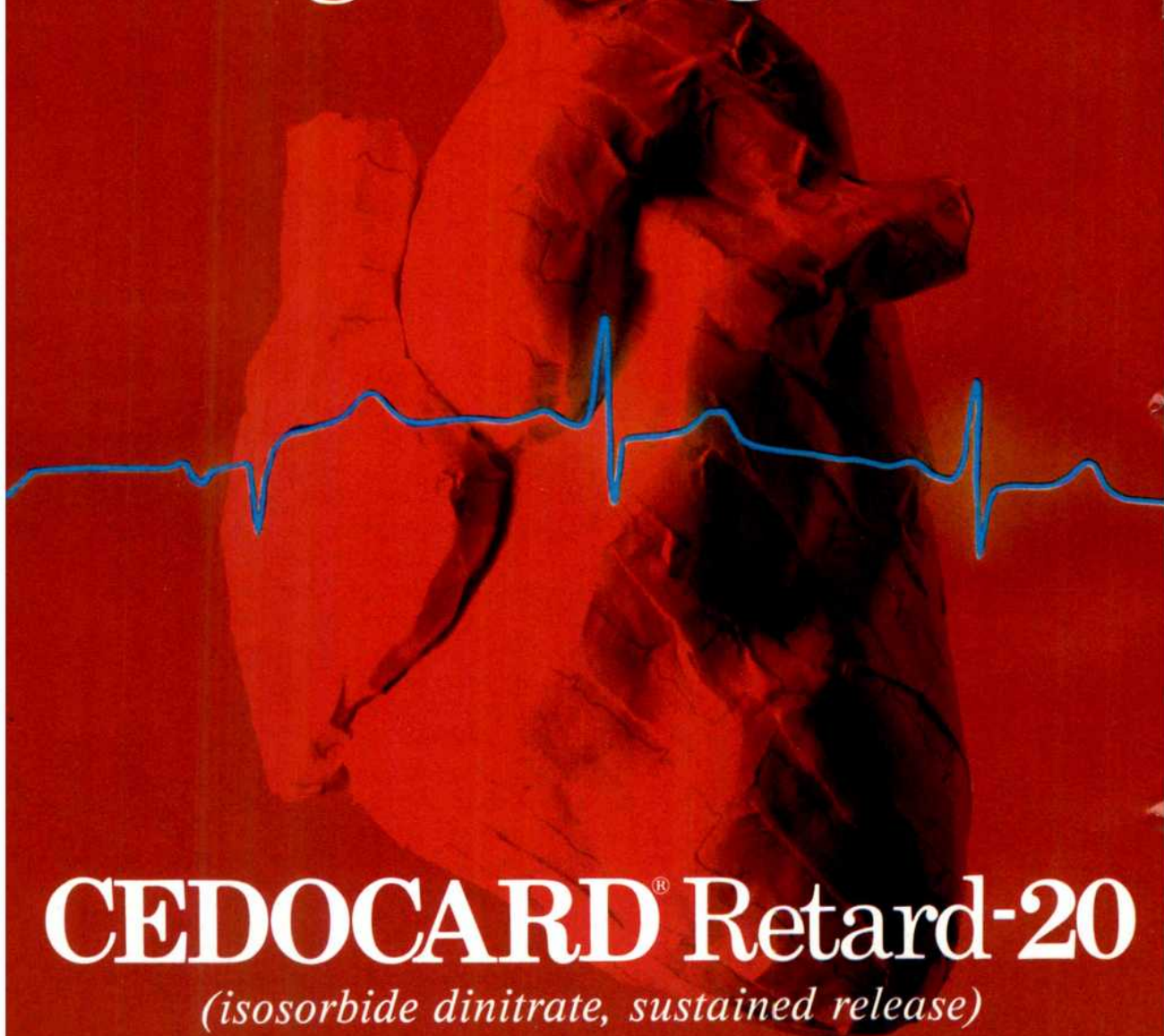


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Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre, London, on Tuesday to Thursday, 26 to 28 November 1985. The President, D G JULIAN, took the Chair during private business. The scientific sessions were under the chairmanship of I R GRAY.

Abstracts of papers

Comparison of prognostic significance of delayed potentials and inducible ventricular tachycardia in 306 survivors of acute myocardial infarction

A R Denniss, D A Richards, D L Ross, J B Uther
Westmead Hospital, Sydney, Australia

The prognostic significance of delayed potentials detected on the signal averaged electrocardiogram and their correlation with inducible ventricular tachycardia were examined in a prospective study of 306 clinically well survivors of transmural myocardial infarction (anterior in 42%) who were aged ≤ 65 years. All patients had both a signal averaged electrocardiogram and programmed stimulation performed 1-4 weeks after infarction. Delayed potentials were present in 26%. The two year probability of remaining free from cardiac death and spontaneous ventricular tachycardia (VT) or fibrillation (VF) was 0.73 for patients with delayed potentials, compared with 0.95 for patients with no delayed potentials ($p < 0.001$) and 0.73 for patients with inducible VT. For prediction of death and VT or VF, delayed potentials had a sensitivity of 66%, a specificity of 78%, a predictive accuracy of 24%, and an odds ratio of 6.7. Inducible VT at programmed stimulation had a sensitivity of 52%, a specificity of 83%, a predictive accuracy of 24%, and an odds ratio of 5.2.

In conclusion (a) delayed potentials present after recent infarction predict a significant risk of death and spontaneous VT or VF; (b) the prognostic significance of delayed potentials is comparable to that of inducible VT at programmed stimulation.

Neurological complications of coronary artery bypass surgery

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University Departments of Cardiology and

Neurology, and the Cardiothoracic Unit, Freeman Hospital, Newcastle upon Tyne

A prospective study has been undertaken to determine the incidence, severity, and functional impact of neurological complications occurring after elective coronary artery bypass graft (CABG) surgery. Three hundred and twelve patients were evaluated over a 12 month period from September 1983 to August 1984 at the Regional Cardiothoracic Centre in Newcastle upon Tyne. A comparison group of 50 patients undergoing major surgery for peripheral vascular disease was also assessed. The patients underwent detailed neurological assessment in the two days before surgery, daily in the early postoperative period, and at intervals in the first six months after surgery. Early postoperative neurological complications developed in 191 of the 312 CABG patients (61%) and included death from cerebral hypoxic damage in one patient (0.3%); prolonged depression of conscious level in 10 (3.2%) patients; definite stroke in 15 (4.8%) patients; ophthalmological abnormalities including retinal infarction, retinal embolisation, or other abnormality of vision in 78 (25%) patients; primitive reflexes in 123 (39.4%) patients; postoperative psychosis in four (1.3%) patients; and peripheral nerve damage (most commonly brachial plexopathy) in 37 (11.8%) patients. Although such a high proportion of the cohort developed detectable changes, serious morbidity or death from neurological damage was uncommon, occurring in only five (1.6%) patients. Follow up of the group of six months after surgery showed a favourable functional neurological outcome in the majority of patients. Minor postoperative abnormalities developed in only nine (18%) of the 50 patients undergoing peripheral vascular surgery and these largely resulted from trauma to lower limb sensory nerves.

Origins of breathlessness in chronic heart failure

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The Cardiothoracic Institute, London

Breathlessness in heart failure is often attributed to raised pulmonary venous pressure. Oxygen consumption ($\dot{V}O_2$), mean pulmonary capillary wedge pressure (PCWP), arterial blood lactate concen-

tration, and pH were measured during treadmill exercise using a slow exercise protocol in 25 men (age 34–67 years) with chronic heart failure (New York Heart Association class II–III). Ten of these patients also performed a rapid exercise test with similar increments of shorter duration. Exercise was terminated due to fatigue in 23/25 patients after the slow test and because of dyspnoea in all patients after the rapid test. Exercise capacity (maximum VO_2 and exercise duration) was not related to resting or exercise PCWP or to the change in PCWP during exercise ($r = -0.38$, $r = -0.19$, $r = 0.12$) nor was there any difference in exercise PCWP within individuals between the two types of tests. Maximum VO_2 , peak cardiac output, and minute ventilation were greater in the rapid exercise test ($p < 0.05$). Peak exercise lactate concentration was higher (3.7 vs 2.2 mmol/l) and the change in pH from the resting state was greater (0.06 vs 0.02 , $p < 0.05$) during the rapid test than during the slow test.

The sensation of breathlessness in chronic heart failure is not simply related to an elevated PCWP but may be due to stimulation of the respiratory centre in response to the metabolic acidosis. Exercise capacity and the symptoms limiting exercise are dependent on the type of exercise test performed. These differences need to be considered when selecting an exercise protocol for studies of drug efficacy in patients with heart failure.

Effects of vasodilators on exercise capacity and myocardial oxygen supply in patients with angina pectoris and normal coronary arteries

R Bugiardini, D Ferrini, M Galvani, C Gridelli, A Pozzati, P Puddu, S Lenzi
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Patients with effort related angina, coronary arteries of normal appearance, and no evidence either of epicardial artery spasm or myocardial hypertrophy have been suggested to have a reduced coronary flow reserve due to inappropriate dilatation of small resistive vessels. Nevertheless whether the ability to dilate may be constrained by a functional or anatomical insufficiency of the microvasculature is poorly understood. To address these questions we selected 15 patients with the above set of findings and a positive (≥ 0.1 mV ST depression) exercise test limited by chest pain. They performed supine bicycle ergometer testing (25 W increments every two minutes) before and during drug induced vasodilatation, which was obtained in five patients with verapamil (10 mg intravenous bolus), in five with

isosorbide dinitrate (10 mg sublingually), and in the remaining with iloprost, a stable prostacyclin analogue (6 ng/kg/min intravenous infusion). Arterial blood pressure and coronary sinus blood flow were simultaneously measured at rest and peak exercise. Compared with control, verapamil significantly ($p < 0.001$) prolonged exercise duration (mean (SD) 510 (74) vs 354 (67) s) and time to onset of 0.1 mV ST depression (393 (50) vs 237 (36) s). Drug administration also resulted in increased coronary blood flow (137 (31) vs 95 (28) ml/min) and in decreased coronary resistance (0.86 (0.15) vs 1.20 (0.24) mm Hg/ml/min) at peak exercise ($p < 0.005$). Conversely no significant changes in exercise capacity and haemodynamics were found following isosorbide and iloprost. Thus effort related angina in patients with normal appearing coronary arteries seems to be mediated by a reduction of coronary flow reserve due to functional rather than anatomical factors. These can be partly counteracted by verapamil. The lack of efficacy of other powerful vasodilators favours an arteriolar dysregulation of calcium uptake as the most likely mechanism.

Natural history of post-myocardial infarction angina pectoris

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St Vincent's Hospital, Dublin, Eire

The natural history of post-myocardial infarction angina pectoris has been examined using a Markov statistical model in 555 male survivors of a first coronary attack at < 60 years followed annually for up to 20 years. Only 21 (4%) had coronary artery bypass operation. Most anginal patients were treated by nitrates alone. In the 130 patients with immediate post-infarction angina, the angina prevalence in survivors reduced to 63%, 44%, 38%, and 36% at 5, 10, 15, and 20 years respectively. The mean survival of these patients was 13.6 years. Angina was present for a mean 5.4 years and absent for a mean of 4.2 years in this group during the first 9.6 years of follow up. After 9.6 years a wide variation in the presence or absence of angina continued with 48% remaining angina free. The 425 patients without initial angina had a mean survival of 15.3 years. They remained free of angina initially for a mean period of 8.1 years. The presence of angina varied during the subsequent 7.2 years of survival with angina being present for 3.8 of these remaining years.

This long term follow up study of post-infarction patients confirms that the presence or absence of angina can vary considerably over time in patients treated medically. These findings have important

implications when assessing the effects of various treatments, including coronary artery bypass surgery, on post-infarction angina.

Isolated coronary ostial stenosis—a previously unrecognised clinical syndrome?

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Coronary ostial stenosis is a rare angiographic finding which we have detected in only 28 (0.6%) of 4427 patients with coronary artery disease. In the majority ostial stenosis was associated with other coronary arterial lesions, but in five patients ostial stenosis was the only lesion present and was not associated with any of the conditions (syphilitic aortitis, Takayasu's aortitis, familial hypercholesterolaemia, aortic valve disease) known to involve the coronary ostia. All five patients were middle aged (38–53) females (two premenopausal); a striking difference from the usual 7:1 male preponderance in atherosclerotic coronary artery disease. Review of the literature shows 11 previously reported cases of which 10 were middle aged women. Angiographic diagnosis can be difficult, but a pressure drop as the catheter tip engages the ostium was a constant finding; lack of spillover of contrast into the sinus of Valsalva may also suggest the diagnosis. The aetiology is unknown and, though it may well be atherosclerotic, the female preponderance raises the possibility of this being a distinct clinical syndrome. All patients had typical exercise related angina and all are now symptom free following saphenous vein internal mammary artery grafting. In one patient the operation was performed at the eleventh week of a successfully completed pregnancy.

Postmortem coronary arteriography following sudden death

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Postmortem coronary arteriography (CA) was undertaken in 75 patients dying suddenly. Seventeen (23%) studies were normal, and in the remaining 58 patients 140 segments were classified according to the angiographic appearance by three independent observers who were in agreement on 122 (87.5%) segments. The results were compared with histology. Plaque fissure (with or without thrombosis) was correctly identified by CA in 45 segments, with a

predictive accuracy of 95% when compared to histology. Old occlusions (with or without recanalisation) were seen in 22 segments (predictive accuracy 90%) and stable plaques or stenoses were seen in 48 segments (predictive accuracy 90%). In 25 patients necropsy identified a clear cause of death outside the heart, in 17 (68%) CA was normal, in 5 (20%) there were "stable" lesions, and in only 3 (12%) were plaque fissures identified. Forty three (86%) of the 50 patients in whom death was presumed to be cardiac had plaque fissures (χ^2 38.5, $p < 0.001$) and a "stable" lesion was seen in the remaining seven.

We conclude that (a) postmortem coronary arteriography compares favourably with histology as a method of categorising coronary artery lesions; that (b) in this study the frequent association of plaque fissures with sudden cardiac death compared with other "stable" coronary lesions supports a causative relation; and (c) that the recognition of plaque fissures identified by in vivo coronary arteriography may influence patient management.

Efficacy of flecainide in the control of ventricular response during exercise in established atrial fibrillation in digitalised patients: its comparison with beta blockade

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The control of ventricular rate in chronic established atrial fibrillation cannot always be effected by digitalis alone, particularly during exercise. Twenty fully digitalised patients in atrial fibrillation with uncontrolled ventricular rate were exercised on a treadmill according to the Sheffield protocol and were divided into two equally matched groups. Ventricular rate control was attempted by the addition of oral flecainide 100 mg twice a day (10 patients) and oral propranolol 80 mg three times a day (10 patients). In the flecainide group improved ventricular rate control was achieved in seven out of eight patients with significant increase in exercise tolerance in five. Two patients were withdrawn from the trial because of drug intolerance. In the propranolol group nine out of 10 patients showed improved ventricular rate control. Only four out of 10 demonstrated improved exercise tolerance.

Our study suggests that flecainide acetate has an important role in the control of ventricular rate in atrial fibrillation in digitalised patients both at rest and during exercise. It parallels the effect achieved by beta blockade, however, with a comparative improvement in exercise potential.

Effect of chronic amiodarone treatment on pulmonary function

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Amiodarone has been reported to cause interstitial pneumonitis or fibrosis, usually with maintenance doses exceeding 400 mg daily. A retrospective investigation of 41 patients receiving amiodarone for a mean of 12.9 months was carried out to determine whether smaller doses commonly affected pulmonary function. The mean maintenance dose was 221 mg daily. At initial pulmonary function testing 11 patients were identified as having an interstitial lung disorder (reduction in transfer factor below 75% predicted value in the absence of significant airflow obstruction and emphysema). Five had an alternative identifiable cause of interstitial lung disorder. Two of the remaining six patients complained of breathlessness since starting amiodarone. Five had no radiological evidence of pulmonary fibrosis. The mean duration of treatment was 21.4 months for patients with interstitial lung disorder, compared with 13.6 months for the remainder. Pulmonary function testing was repeated eight to 14 months later in 37 patients. Four of the initial six patients with interstitial lung disorder still had a reduction in carbon monoxide transfer factor to less than 80% of that predicted. One of the two with now normal pulmonary function had discontinued amiodarone. There were no new cases of interstitial lung disorder.

It is concluded that an interstitial lung disorder may be present in symptom free patients with normal radiological assessment receiving low dose amiodarone. Follow up longer than one year will be necessary to assess fully the effect of amiodarone on pulmonary function.

Temporary transvenous cardioversion for recurrent ventricular tachyarrhythmias

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Recurrent ventricular tachyarrhythmias (VT/VF) occurring within the first 12 hours after myocardial infarction pose several problems: these include repeated general anaesthetics, delays before cardioversion, and superficial burns. Nevertheless, long term prognosis can be good in those patients who survive this acute phase. We have investigated the

efficacy of DC shocks of varying energies (0.5 J to 25 J) generated by a Cardioverter (Medtronic model 5350) and delivered to the right ventricular endocardium for the treatment of ventricular tachyarrhythmias. Insertion of a specially constructed temporary lead was attempted in 11 patients (six men and five women, age range 55–72 years) because of recurrent VT in five and VF in six. In all but two patients these arrhythmias complicated acute myocardial infarction. In nine the lead was inserted without difficulty, but lack of stability (one case) and provocation of ventricular fibrillation (one case) prevented placement by skilled operators in two patients. Successful cardioversion was achieved on 25 separate occasions. The energy required varied from 0.05 J to 15 J (mean 6.8 J). Low energy shocks (0.05–5 J) failed on two occasions (one case of ventricular tachycardia and one case of ventricular fibrillation) but medium energy shocks (10–15 J) were uniformly successful. Energies needed for conversion of ventricular tachycardia (mean 4.6 J) tended to be lower than for ventricular fibrillation (mean 10.3 J). No evidence of myocardial damage was detected as a result of repeated shocks in two patients who subsequently died of intractable heart failure. Although the present lead can be difficult to insert, our experience suggests that temporary transvenous cardioversion can be a safe and effective method for treating recurrent ventricular tachyarrhythmias, offering some advantages over conventional methods.

Ischaemia and sinus node disease

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Sinus node disease is one of the commonest conditions requiring pacemaker treatment yet its aetiology is still uncertain. Initially it was thought to be ischaemic in origin but latterly this has been disputed. We report a study of the sinus node and atrial blood supply in patients with chronic sinus node disease by necropsy angiography. The hearts were injected with Chromopaque that fills vessels down to arteriolar size. The right coronary artery was injected first and radiographs were taken in three planes. The left coronary artery was then injected with a different coloured dye and further radiographs were taken. Subsequently the sinus node was examined histologically by serial section. The findings in 23 cases of chronic sinus node disease were compared with those in 59 cases with normal sinus node function. In 19 patients with sinus node disease the sinoatrial node artery filled normally with no evidence of

narrowing either of the artery itself or of the parent coronary vessel. The sinoatrial node artery filled partly or not at all in four cases. In three other hearts with normal sinus node arterial filling there were gross networks of collateral vessels supplying the territory of the contralateral coronary artery which was obstructed at its origin, circumstances that are compatible with a vascular steal.

Interferences from necropsy data about function during life must be made with caution. It seems likely, however, that our methods overestimate rather than underestimate the importance of arterial lesions. With these reservations it is suggested that in our material ischaemic heart disease was unlikely to have been the aetiological factor in the majority of patients but probably was important in a significant proportion.

The familial recurrence of congenital heart disease

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In a five year study 1021 patients have been referred for fetal echocardiography because of a family history of congenital heart disease. The index case was one previously affected child in 384 cases; two affected children in 30 cases; three affected children in two cases; an affected parent in 41 cases; an affected second degree relative in 39 cases; the relationship of the affected index case was unknown in 25 cases. The index case was male in 56% of cases and had died in 68%. The overall recurrence rate was 20 cases—17 in cases where the index case was one affected child and three in cases where the index case was two affected children. This gives recurrence rates of 1 in 52 and 1 in 10 respectively. There were no recurrences in the other groups. There was an increased tendency to refer mothers when the previous child had died, and mothers of index cases with severe defects were disproportionately selected for referral. Hypoplastic left heart syndrome was the most frequent diagnosis in the index cases. Even allowing for this, left sided lesions showed an increased risk of recurrence. So also did complex anomaly of the type commonly associated with atrial isomerism. It appears that some forms of congenital heart disease are more likely to recur within a family group than others. Although the recurrent lesion was concordant or similar in 13 of the 20 recurrences, in the remaining seven cases the severity of the recurrent lesions differed from that in the index case.

Prevalence of hypertension in habitually salted-tea drinking population in Northern Kashmir

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Numerous epidemiological, clinical, and experimental studies have suggested that a high salt intake is causally related to the incidence of hypertension. Many of these studies have been criticised, however, mainly because environmental factors have received less emphasis than salt. Western civilisation of an area or migration into a "civilised" area must bring into play a constellation of environmental, cultural, dietary, and economical factors in addition to salt that may influence blood pressure. In this study we attempted to explore the relation between salt and blood pressure in a salted-tea drinking population of Northern Kashmir that has not been exposed to a Western way of life. All the available family members of randomly selected houses in 14 villages were studied. Dietary intake was documented for the whole month of the study period to estimate the daily salt consumption in 313 subjects (210 males, 103 females). Their age ranged from 15 to 85 years (median 35) and their mean daily salt intake was 150 (52) mmol (range 80–440). Both the systolic and diastolic blood pressures showed a significant increase with salt intake and age; multiple regression analysis suggested an independent effect of salt intake on blood pressure after adjusting for age. Fifty nine (18.8%) subjects had hypertension (blood pressure $\geq 145/100$ mm Hg); their daily salt intake was significantly higher than that of normotensive subjects (186 (66) *vs* 141 (44) mmol; $p < 0.001$). These studies suggest a relation between habitual high salt intake and essential hypertension.

Factors influencing survival and mode of death in chronic ischaemic cardiac failure

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A consecutive series of 50 patients (40 males, 10 female) aged 57 (7) years (mean (1 SD)) with severe chronic ischaemic cardiac failure for more than three months was followed for 17.7 (10.8) months. The mean left ventricular ejection fraction for the group was 0.28 (0.14), and all patients were receiving intensive medical treatment—daily dose of frusemide 121 (139) mg; 44 were on digoxin and 28 were

on vasodilator drugs. During follow up four patients have successfully undergone cardiac surgery and medical treatment was modified in the majority of patients, with four patients receiving antiarrhythmic drugs. Twenty six patients died, 17 suddenly within one hour of onset of symptoms and nine of progressive cardiac failure. Mortality was 28% at one year and 69% at two years. Multivariate analysis showed that death was most likely to occur in patients with the poorest left ventricular ejection fraction (survivors 0.35 (0.14) *vs* deaths 0.20 (0.08) ($p < 0.005$)) and in patients with the most serious ventricular arrhythmias on ambulatory electrocardiographic monitoring (survivors (Lown score) 1.9 (1.2) *vs* deaths 3.4 (1.6) ($p < 0.05$)). No differences were detected in ejection fraction and Lown score between sudden and non-sudden deaths. Several variables did not statistically influence survival or mode of death; these included age, duration of cardiac failure, number of myocardial infarctions or diseased coronary vessels, pulmonary capillary wedge pressure, New York Heart Association functional class, cardiothoracic ratio, exercise capacity, and intensity or type of drug treatment. Thus to determine the prognosis in severe cardiac failure, reliance cannot be placed on the above variables. Assessment of left ventricular ejection fraction and ambulatory electrocardiographic monitoring are the best predictors of survival. None of the above variables predicted the mode of death.

Infective endocarditis: current incidence and mortality

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One hundred and eighty two cases of infective endocarditis in the North East Thames Region were studied over two and a half years. This gives a minimal annual incidence of 21 cases per million and probably underestimates the true figure by only 15–20%. Overall mortality was 21% (39 deaths). Subgroup mortality was *Streptococcus viridans* infection 7% (6/82), age under 60 years 9.5% (10/95), age 60 or over 34% (28/82), *Staphylococcus aureus* infection 31% (8/26), prosthetic valve endocarditis 53% (10/19), and *Staph epidermidis* infection 67% (8/12). *Strep viridans* was the commonest infecting organism (45%) and dental procedures (15%) or dental sepsis (12%) were the commonest causative events. Drug abuse (7%) and cystoscopy (3%) were the most frequent amongst other specific causes. No cause was found in 50% of cases. There were no

cases of failure of antibiotic prophylaxis, but in nine patients endocarditis followed inappropriate omission or maladministration of prophylaxis. Mitral valve involvement was more frequent than aortic (53% *vs* 37%) and had a lower mortality (21% *vs* 28%). Underlying pathology was rheumatic (20%), mitral prolapse (19%), bicuspid aortic valve (10%), congenital (6%), and unknown in 35%. Echocardiographic detection of vegetations in 50% of those investigated (139 patients) was not associated with an increased mortality. Surgery carried a mortality of 7% (2/29) in native valve infection but 80% (4/5) in prosthetic valve infection. It is likely that surgical intervention lowers the mortality associated with native valve infective endocarditis. Earlier diagnosis and operation might have improved the outcome in six of the 37 patients who died. A reduction in incidence might occur with correct use of antibiotic prophylaxis and improved dental health.

Exercise capacity and heart rhythm following transvenous fulguration of atrioventricular conduction

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Twenty four patients, aged 19–67 years, were studied 4–36 (mean 17) months after transvenous fulguration of the atrioventricular junction to assess exercise capacity and spontaneous heart rhythm. Fifteen patients had had atrioventricular re-entrant tachycardia and nine patients, four with mitral valve disease and five with the "brady-tachy" syndrome, had had an uncontrollable ventricular response to atrial fibrillation or flutter. 1 to 3 direct current shocks of 200–400 J were delivered via a His bundle electrode in each case. After fulguration, 17 patients had complete and five partial atrioventricular block. In two patients sinus rhythm was maintained via an accessory atrioventricular pathway. Though all patients were free of palpitation after the procedure, 10 developed exertional dyspnoea, and pre-existing dyspnoea worsened in two patients. Twenty three patients underwent exercise testing during ventricular demand pacing at 60 or 70 beats per minute using the Bruce protocol. Exercise time was reduced to 45 (23%) (mean (SD)) of the predicted value for their age and sex. In six patients with complete heart block there was an increase in ventricular rate during exercise. In three patients with partial heart block the degree of atrioventricular block increased on exercise. The 13 patients with rate responsive pacemakers (DDD or TX) demonstrated a significantly better but still impaired exercise capacity during

physiological pacing (67 (24)%) as compared with their performance during fixed rate pacing (41 (18)%) ($p < 0.001$).

We conclude that though the procedure is successful in controlling tachycardia it may cause a reduction in exercise capacity. Most patients remain in complete atrioventricular block after the procedure and, in contrast to the practice as described in early reports, would benefit from "physiological" pacing; though even with this mode exercise is likely to be abnormal.

Eleven years' experience of pacemaker insertion and therapy in a cardiothoracic centre

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Six hundred and five patients had a first pacemaker implantation between 1970 and 1980. All but one had single lead ventricular systems. All deaths were known as patients were indexed with the census authorities. Probability of survival was calculated and the significance of differences between groups was assessed by Wilcoxon's signed rank test. There were 312 males and 293 females, 373 (62%) aged over 70 years, 146 (24%) aged 60-70 years. Five-hundred and nineteen (87%) were symptomatic. Of these, 346 (67%) had syncope, 91 (17%) suffered near syncope or dizzy spells, and 61 (12%) were dyspnoeic. Three hundred and eight (51%) have died. Women had significantly better survival than men ($p < 0.05$). The probability of surviving one year was 0.84 for males (0.92 for females), three years 0.68 for males (0.79 for females), five years 0.56 for males (0.65 for females), and ten years 0.22 for males (0.37 for females). The probability of five year survival was 0.6 in symptomatic patients. In 286 patients with complete atrioventricular dissociation the probability of five year survival was 0.63 while in 84 patients with electrocardiographic evidence of sick sinus syndrome it was 0.55 (NS). In England and Wales the probability of surviving five years at age 75 is 0.61 for males (0.76 for females).

It is concluded that patients having a pacemaker implantation have a similar expectation of life as the normal population. Patients with complete atrioventricular dissociation surprisingly had a similar probability of five year survival as those with sick sinus syndrome.

Low energy endocardial countershock for the treatment of ventricular tachycardia and fibrillation

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Low energy endocardial countershock (microshock) was used in 15 patients, aged 33 to 67 (mean 53) years, with ventricular tachycardia. Five of the patients were receiving antiarrhythmic drugs. A special large surface area lead, with its active tip in the right ventricle and the indifferent electrode in the right atrium or superior vena cava (10 patients) or in the inferior vena cava (five patients), was used with either an attenuated QRS synchronous defibrillator or with a special unit triggered by endocardial signals. Sixty eight shocks (10 to 6700, mean 1138 mJ) were used for ventricular tachycardia. Nine patients were successfully treated (20 shocks) with no apparent difference between the two sites used for the indifferent electrode (right atrium or superior vena cava (six); inferior vena cava (three)). Further microshock in the remaining six patients was limited by pain or by degeneration to ventricular fibrillation. Proarrhythmic effects included atrial fibrillation in one patient, acceleration of ventricular tachycardia in two, and ventricular fibrillation in five. Pacing with bursts and extrastimuli was effective in eight patients (five of the nine in whom microshock was successful and three of the other six). Pacing caused ventricular fibrillation in one patient and accelerated tachycardia in two. Microshock (5000 mJ) was effective for ventricular fibrillation in one of three patients.

In conclusion, pacing was safer but slightly less effective than microshock for the treatment of ventricular tachycardia, but their combined use allowed successful treatment in more patients than with either alone. Microshock may occasionally be effective for ventricular fibrillation.

Conduction between donor and recipient atria following orthotopic cardiac transplantation

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The relations between mechanical and electrical activity of donor (D) and recipient (R) atria were analysed in 61 unselected patients undergoing annual reinvestigation after orthotopic cardiac transplantation. Close correlation between the two atria was observed in 10 (16%) patients who comprised the subjects of this study. There were nine males and one female, with a mean age at transplantation of

46.9 years. The mean age of the donors was 21.3 years. Immunosuppression was achieved with steroids and azathioprine in eight patients two of whom had cyclosporin added after two years; the remaining two patients received only cyclosporin and azathioprine. The frequency with which the correlation was observed increased from 4% at one year to 66% at five years after transplantation. Electrophysiological studies showed a constant relation between the donor atrial electrogram (DE) and the recipient atrial electrogram (RE), with the DE preceding the RE at rest. The interval between DE and RE varied from 80 ms to 240 ms (mean 145 ms). This relation remained constant during incremental donor atrial pacing, with two patients developing 2:1 block at rates of 170 and 130 beats per minute. Recipient atrial pacing showed conduction from R to D in six of the eight tested. The functional refractory periods of the D to R pathway, derived by atrial premature stimuli in five patients, ranged from 280 ms to 430 ms (mean 328 ms) with two of these patients having significantly shorter effective refractory periods.

It is concluded that electrical conduction can occur across the suture line after transplantation. This has important clinical implications.

Four dimensional cardiac imaging

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A system for the production of a four dimensional (moving three dimensional) epicardial left ventriculogram modelled and highlighted to show regional wall motion is described and demonstrated. The computer generated moving imaging is derived by fitting a surface to the three dimensional coordinates of coronary artery bifurcations. These are determined by analysis of digitised biplane coronary cine-angiograms that have been calibrated within a defined external coordinate system and corrected for pincushion distortion. The derived three dimensional data points are then interpolated and the resulting surface, which is lit from a point source, may be viewed from any angle. The coronary arteries are then superimposed to aid orientation and interpretation. Successive frames through the cardiac cycle may be displayed in sequence at any speed, thus producing cardiac wall motion.

This image system not only provides a unique three dimensional view of left ventricular activity but also, since the positions of all the data points at any time are known, measures may be made of wall velocity, acceleration, rotation, and torsion (either with reference to the external coordinate system or to

a computed time dependent internal coordinate system). The changes in these measures of wall motion are displayed in the three dimensional image as different colours.

Magnetic resonance quantification of atrial shunting and valvar regurgitation

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We have previously shown that both left and right ventricular volumes can be measured accurately by magnetic resonance. The purpose of this study is to quantify valvar regurgitation and left to right shunting through an atrial septal defect by comparing left and right ventricular stroke volumes, which should be identical over the period of imaging in the absence of regurgitation or shunting. Fifteen patients were studied by magnetic resonance, first pass and equilibrium radionuclide angiography, and cardiac catheterisation. Multiple transverse magnetic resonance images were acquired at end diastole and end systole using a Picker International machine operating at 0.24 tesla and using a spin echo sequence with an echo time of 24 ms. Ventricular volumes were calculated by summing their areas in the contiguous 1 cm sections. In 20 normal subjects the mean left to right ventricular stroke volume ratio was 1.01 (SD 0.067), thus establishing a normal range of 0.88–1.14. In five patients with atrial septal defect the stroke volume ratio was abnormal and the correlation coefficient between magnetic resonance and oximetric determination of the ratio of pulmonary flow to systemic flow was 0.91. In five patients with mitral regurgitation and five with aortic regurgitation the stroke volume ratio was also abnormal, and the degree of abnormality was similar to semi-quantitative assessment by x ray angiography. The correlation coefficients between magnetic resonance and radionuclide values of left ventricular ejection fraction, right ventricular ejection fraction, and stroke volume ratio were 0.88, 0.88, and 0.82 respectively. The radionuclide measurements underestimated right ventricular stroke volume, however, especially in the patients with atrial septal defect and a dilated right heart, because of overlap of right atrium and ventricle in the left anterior oblique projection.

Magnetic resonance provides a non-invasive method to quantify valvar regurgitation and atrial shunting, and may improve the assessment of such patients.

Detection of coronary disease: a comparison between exercise technetium ventriculography and exercise thallium imaging

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Radionuclides have become widely used for the detection of coronary artery disease. In this study we compared gated exercise technetium scans at rest and during maximal supine exercise and post-exercise gated thallium imaging in 50 male patients undergoing routine coronary angiography. The mean age of the patients was 48.8 years (range 33–67 years); eight had normal coronary arteries, nine had single, 20 had double, and 13 had triple vessel disease. Both radionuclide investigations were performed within 48 hours of coronary angiography. Exercise testing was maximal symptom limited and performed on a bicycle ergometer. Thallium was injected intravenously 30 s before termination of exercise and images were obtained in three projections gated to the electrocardiogram. Gated technetium scans were obtained in a 30–45° left anterior oblique projection with a 5–10° caudal tilt at rest and at peak exercise. Technetium scans were analysed for regional wall motion abnormalities occurring at rest or on exercise and also for the left ventricular ejection fraction response to exercise. Left ventricular ejection fraction response to exercise was assessed with normal values from 14 healthy volunteers; a failure to increase the left ventricular ejection fraction by $\geq 3\%$ on exercise was considered to be abnormal. The presence of a regional wall motion abnormality or an abnormal left ventricular ejection fraction response was considered indicative of coronary artery disease. This provided a sensitivity of 78%, a specificity of 75%, and a predictive accuracy of 78%. Thallium scans were analysed visually and the presence of a defect was considered indicative of underlying coronary disease. This provided a sensitivity of 100%, a specificity of 75%, and a predictive accuracy of 96%. These results show that exercise gated thallium imaging is superior to exercise gated technetium ventriculography and therefore is the investigation of choice in the detection of coronary artery disease.

Myocardial imaging with iodine-123 meta-iodobenzylguanidine

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Iodine-123 meta-iodobenzylguanidine, an analogue of guanethidine, is taken up by sympathetic nerves in a similar manner to noradrenaline. It has been used to detect and to treat phaeochromocytoma. In this study we report our experience is using this tracer to image catecholamine uptake into myocardial sympathetic neurones. 125 MBq of the tracer was injected intravenously in 10 subjects and imaging was performed 30 minutes later. Planar images were obtained in five subjects and tomograms in five. For planar imaging, 500 000 counts were collected in anteroposterior and left anterior oblique projections. Tomograms were reconstructed from 32 images, each of 30 s collected over a 180° arc. In two subjects there was no myocardial uptake. Both had phaeochromocytoma with raised plasma noradrenaline concentrations. Tracer uptake was apparent in eight subjects. In seven this was uniform throughout the myocardium, but in one there was a defect corresponding to a previous myocardial infarction.

Myocardial imaging with iodine-123 meta-iodobenzylguanidine is feasible. In our early experience uptake is reduced in conditions of catecholamine excess or after myocardial infarction. This approach should permit examination of myocardial sympathetic nerve function in myocardial disease.

Segmental wall motion analysis of cross sectional echocardiograms; its reproducibility and sources of variability

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Subjective analysis of left ventricular segmental wall motion is widely used to assess regional left ventricular function and the effects of interventions in patients with ischaemic heart disease. To determine its reproducibility we studied 20 consecutive men with proven ischaemic heart disease and 10 age matched controls. Standard parasternal, apical, and subxiphoid views were attempted in all subjects by two echocardiographers, and echoes were reported by two analysers, each on two occasions. The left ventricle was subdivided into five segments, and wall motion was scored as normal, hypokinetic, akinetic, dyskinetic, or inadequately visualised. The different sources of variability were evaluated. The echocardiographers contributed little variability, the frequency and reproducibility of reporting being the same for echoes from each echocardiographer except for subxiphoid echoes where more segments were

reported to be abnormal by one of the echocardiographers (45% *vs* 27%). Within and between analyser variability was large. Replicate analysis of the same segment showed within analyser agreement of 92% for one analyser but only 80% for the other. Between analyser agreement was 89% for some segments but only 63% for others and was best in those segments where both analysers infrequently reported abnormal wall motion. Reporting bias is thus an important variable.

The subjective assessment of regional left ventricular function thus has major limitations particularly for use in longitudinal studies.

"Physiological" tricuspid and pulmonary regurgitation: their varying incidence in a representative adult cardiac population

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Peak systolic right ventricular pulmonary artery pressure and pulmonary artery end diastolic pressure can be accurately evaluated by Doppler if both complete forward and regurgitant flow wave forms can be recorded across both the tricuspid and pulmonary valves. In our experience both pulsed and continuous wave Doppler echocardiography frequently demonstrate tricuspid and pulmonary valve regurgitation in normal individuals. To determine the precise incidence of "physiological" right heart valve incompetence in a representative adult cardiac population (and thus the frequency with which right heart pressures could be estimated), we analysed consecutive complete Doppler echocardiographic studies of 413 patients undergoing routine investigation. No patient had auscultatory evidence of tricuspid or pulmonary valve incompetence. Tricuspid valve regurgitation was best recorded by a through transducer continuous wave Doppler technique and was present in 46% normals, 57% of those with ischaemia (with ejection fraction $> 60\%$), 73% patients with cardiomyopathy, 81% with mitral or mixed left heart valve disease, 76% patients with isolated aortic disease, and in 87% with mitral or aortic prostheses. In contrast, pulmonary valve regurgitant wave forms were best recorded by a pulsed wave Doppler technique and they were present in 58% normals, 71% with ischaemia, 73% with cardiomyopathy, 84% with mitral or mixed left heart valve disease, 72% with aortic disease, and in 89% with aortic or mitral prostheses. The "physiological" tricuspid and pulmonary regurgitation

present in these patients could be differentiated from functional regurgitation studied in a further 52 patients by (a) absence of murmur, (b) Doppler signal strength, and (c) width and length of jet. In conclusion "physiological" tricuspid and pulmonary regurgitation are normal findings in about half the normal population but they occur more frequently in patients with cardiac disease, in whom their incidence is related to the cardiac lesion. Simultaneous correlative catheter/Doppler studies confirmed that these wave forms will allow accurate right heart pressure evaluation in $> 71\%$ of patients with cardiac disease.

Two dimensional and pulsed Doppler investigations of children with early systolic murmurs

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An early systolic murmur localised to the lower left sternal border is generally regarded as a sign of a persistent small ventricular septal defect. Twenty children aged from 4 to 15 years were studied by cross sectional and pulsed Doppler ultrasound. Nine had been documented earlier as having a pansystolic murmur and two had had evidence of a large shunt (cardiomegaly or breathlessness). In eight of the 20 patients the early systolic murmur was confined to or accentuated in inspiration. Cross sectional studies showed a pseudoaneurysm of the membranous interventricular septum or adherence of tricuspid valve tissue in 17. Pulsed Doppler examination did not show evidence of persistent left to right ventricular shunt in any patients. Seventeen patients showed a Doppler signal consistent with early systolic reflux through the tricuspid valve. Two of the three patients who did not show this had murmurs heard only in inspiration.

It is suggested that the early systolic murmur of a "closing ventricular septal defect" is caused by tricuspid reflux produced by incorporation of the septal cusp of the tricuspid valve in the defect and that the defect is at that stage completely closed.

Doppler estimation of pressure gradient in infundibular pulmonary stenosis

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The validity of Doppler ultrasound in estimating the gradient in patients with pulmonary valve stenosis is now accepted, but there is little information of its use in infundibular stenosis where energy losses due to friction might invalidate the modified Bernoulli equation. The report reviews our experience in comparing Doppler estimation of pressure gradient with that measured at cardiac catheterisation in 24 children (aged 7 days to 16 years, mean 2.6 years) with pulmonary infundibular stenosis, including 13 with tetralogy of Fallot. Various parasternal and subcostal positions were explored to obtain maximum velocity of blood flow and the obstructive gradient was calculated from the modified Bernoulli formula. The gradient across the obstruction could be measured directly at the time of catheterisation in only 17. Comparison of the Doppler results and the measured gradient showed a good correlation with measurements made on catheter entry ($r=0.94$) but a poorer one with measurements made on withdrawal ($r=0.79$). Doppler ultrasound, by measuring the total gradient from the right ventricle to the pulmonary artery, provides an accurate non-invasive assessment of the severity of pulmonary stenosis and in those with infundibular obstruction allowance need not be made for possible energy losses due to the elongated nature of the obstruction or narrowing at more than one level.

Effect of nitrates on coronary re-occlusion during intracoronary thrombolysis

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The relative roles of thrombosis and coronary vasoconstriction in the pathogenesis of acute myocardial infarction are poorly understood. We performed coronary arteriography in eight patients (on nine occasions) within two hours of the onset of sustained ST elevation (group 1) and in 10 patients 2–4 hours after the onset of continuous chest pain associated with ST elevation (group 2). All patients had coronary occlusion which failed to open with intracoronary isosorbide dinitrate 2mg and after this thrombolysis was attempted with intracoronary streptokinase at 5000 IU/min. The artery was patent at the end of the procedure in six instances in group 1, with no subsequent development of pathological Q waves in five of these, and in eight patients in group 2 all of whom developed Q waves (χ^2 4.94; $p<0.05$). Spontaneous, intermittent reopening and

re-occlusion of the vessel during continuous streptokinase infusion were seen in five instances in group 1 and in two patients in group 2. In four patients (two in group 1 and two in group 2) intracoronary isosorbide dinitrate re-established transient patency of the re-occluded artery. In six patients in group 2 partial reopening was achieved by streptokinase alone but distal filling and runoff of contrast medium were poor. In this group, however, further intracoronary isosorbide dinitrate resulted in patency of the artery in eight patients with normal filling and run off contrast medium in six.

Intermittent arterial reopening and re-occlusion are seen both before myocardial infarction and during its acute evolution. Interaction between intraluminal thrombosis and coronary vasoconstriction appears to perpetuate the coronary occlusion. Combined thrombolytic and nitrate therapy increases the rate of coronary recanalisation and, when given very early, may prevent myocardial infarction.

Follow up to two years in 108 patients with severe early cardiac infarction treated with intravenous streptokinase

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One hundred and eight patients with early (less than six hours) severe (Peel index >12) cardiac infarction were treated with intravenous streptokinase (1.5 million units). One hundred and three patients were studied by coronary angiography (or at necropsy) and 79% had a patent infarct-related artery (patent group). Twenty one per cent showed persistent coronary occlusion or initial patency followed by reocclusion (occluded group). One hundred per cent follow up was obtained up from 3 to 24 months (mean 11.6 months). There was one hospital death (1.2%) in the patent group and four (19%) in the occluded group ($p<0.05$). During follow up there were four deaths in the patent group (4.9%) and none in the occluded group (NS). No deaths occurred in those treated with surgery (5.6%) or percutaneous transluminal coronary angioplasty. Those with an occluded infarct-related artery were more likely to have disabling cardiac symptoms at follow up (25% vs 40% in New York Heart Association class III or IV, $p<0.01$), were significantly more likely to be disabled by angina (37.5% vs 13.3%, $p<0.05$) but not by dyspnoea, and were more likely to have required urgent hospital admission (41.2% vs 12.0%, $p<0.01$). In the patent group

48% had been unable to resume their former occupation compared with 43% (NS) in the occluded group.

In conclusion successful coronary reperfusion with intravenous streptokinase conferred a significant advantage with respect to hospital mortality that appeared to be maintained during follow up. Failure of coronary reperfusion was associated with a worse symptomatic status, more disabling angina, and greater likelihood of hospital admission during follow up.

Percutaneous transluminal coronary angioplasty—results in patients with acute myocardial infarction

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The place of percutaneous transluminal coronary angioplasty (PTCA) in the treatment of acute myocardial infarction remains controversial. In our first 24 patients (20 men and 4 women, mean age 51 years) undergoing PTCA related to an acute myocardial infarction, PTCA was performed only in the infarct related vessel and was attempted in 18 lesions (seven occlusions) in anterior descending arteries, one in a circumflex artery, and 11 (five occlusions) in right coronary arteries. Up to three sequential lesions in any one individual were successfully dilated. Primary success (reduction in stenosis without associated emergency bypass grafting was achieved in 26 (87%) of these lesions (stenosis reduced from 90 (14)% (mean (SD)) to 30 (29)%, $n=30$). Two (8%) patients went on to emergency bypass grafting, and one patient (who underwent PTCA during active external cardiac massage) died five hours after successful dilatation of an anterior descending artery occlusion. All six patients with dilatations within 1.5 hours of the onset of chest pain have normal residual left ventricular function (peak creatine kinase 324 (130) U/l, ejection fraction 67 (5)%). No improvement in left ventricular function was demonstrable in patients reperfused three hours or more after the onset of acute myocardial infarction (peak creatine kinase 1755 (690) U/l, ejection fraction 47 (9)%). In follow up of 3–15 months one patient had a further acute myocardial infarction at two weeks post-PTCA and one has angina. A further three patients have symptomatic left ventricular impairment. Two thirds (16/24) of patients have had an uneventful recovery with return to normal life.

PTCA in acute myocardial infarction can be performed with acceptable risk. These preliminary results suggest that preservation of left ventricular function is only likely in the very early stages of myocardial infarction and that after two to three hours PTCA might only be indicated in the presence of continuing ischaemic chest pain.

How many patients with myocardial infarction are suitable for thrombolysis?

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Thrombolytic therapy is now widely advocated in the management of acute myocardial infarction (AMI). To be of benefit treatment should be initiated within six hours and preferably be applicable to a majority of patients. 403 patients were considered for entry into a trial of intravenous streptokinase in suspected AMI. 36 (9%) were entered into the trial. The reasons for the exclusion of the remaining 367 (91%) are as follows. 260 (65%) were excluded because they failed to meet the inclusion criteria: 157 (39%) presented later than six hours, 19 (5%) had atypical symptoms, and 84 (21%) did not demonstrate ST elevation. 143 (35%) patients fulfilled the inclusion criteria. 45 had contraindications to thrombolysis. Thus 98 (24%) patients were suitable for participation in the trial. Of these, 42 (10%) were over 70 years, the upper age limit. Thus, according to this trial protocol, 56 (14%) patients were suitable for thrombolysis and therefore eligible for recruitment. Two died before randomisation, six refused consent and twelve were not randomised for administrative reasons. 36 (9%) patients were therefore randomised. In view of the current enthusiasm for thrombolysis, these data suggest that such treatment may only be applicable to a small number of patients with AMI.

Assessment of regional myocardial shortening using routine diagnostic coronary arteriograms

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Regional myocardial shortening has been studied using epicardial markers implanted at operation and

this has been correlated with abnormalities of regional wall motion on left ventricular cineangiogram. Coronary artery branch junctions have also been used as epicardial markers but this has involved biplane cineangiography and three dimensional computer graphics. We have analysed coronary artery shortening in one plane and correlated this with normal and abnormal left ventricular cineangiograms in the same plane. Nineteen patients with normal and 19 with abnormal left ventricular cineangiograms were studied. Both left ventricular and left anterior descending coronary artery shortening were assessed in the 30° right anterior oblique view using septal branches and the end bifurcation of the left anterior descending coronary artery as epicardial markers. Frame by frame contours of the left anterior descending coronary artery were drawn and the left ventricle was drawn in end diastole and end systole. The anterior wall and apex were divided into three segments and left anterior descending artery was divided into corresponding proximal, middle, and distal portions. The mean percentage total left anterior descending coronary artery shortening of the normal group compared with that of the abnormal group was 15.06 (7.3)% *vs* 9.3 (5.2)%, ($p < 0.01$). There were also significant differences for the distal (15.2 (6.3)% *vs* 4.4 (9.9)%, $p < 0.01$), and middle (24.1 (8.1)% *vs* 16.7 (7.9)%, $p < 0.01$) portions but not the proximal portion. The correlation with left ventricular cineangiographic score was $r = -0.72$ ($p < 0.01$) for the total percentage shortening and $r = -0.76$ ($p < 0.01$) and $r = -0.67$ ($p < 0.01$) for the distal and middle portions respectively.

This relatively simple technique of assessing myocardial shortening may be of use when repeated left ventricular cineangiograms are not desirable such as during thrombolytic treatment or percutaneous transluminal coronary angioplasty.

Functional effects of regional left ventricular asynchrony during acute angina

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To study the effects of angina on regional energy transfer from myocardium to circulation simultaneous left ventriculograms and high fidelity pressure traces were recorded in 12 patients at rest and during pacing induced angina. Pressure-volume loops were constructed together with isometric plots of regional

wall motion and corresponding pressure-displacement plots in the form of loops. Global and local work was derived from respective loop areas; cycle efficiency was defined as the ratio of a loop area to the product of total pressure change and wall displacement. Angina did not cause significant change in pressure-volume loop area or efficiency or in end systolic pressure volume relations, though diastolic pressure rose. Major regional effects were seen, however. In the ischaemic area in four cases loop area fell due to a drop in the amplitude of displacement but the loops remained synchronous and efficiency was maintained. In eight cases there was a striking fall in regional efficiency due to the development of asynchrony; inward wall motion being delayed by up to 160 ms with respect to minimum left ventricular volume. In seven cases a similar reduction of efficiency was seen in distant non-ischaemic areas due to premature cessation of inward wall motion by up to 120 ms with respect to minimum left ventricular volume and partial or complete outward wall motion before mitral valve opening. Thus the overall pressure-volume relation is insensitive in detecting the effects of angina on left ventricular function. The major disturbance is loss of synchronous wall motion in both ischaemic and distant segments leading to reduced efficiency of energy transfer from myocardium to circulation.

Comparison of ejection dynamics in hypertrophic cardiomyopathy and valvar aortic stenosis

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Previous studies in hypertrophic cardiomyopathy showed that the proportion of the stroke volume ejected in early and late systole was similar in patients with and without left ventricular gradients. We have compared the ejection dynamics in 15 patients with valvar aortic stenosis (gradient 50–130 mm Hg, mean 75) and 15 with hypertrophic cardiomyopathy who were matched for age, sex, and magnitude of resting systolic gradient (50–130 mm Hg, mean 81); 30 normal subjects were also studied. Technetium-99m equilibrium cineangiography was performed, time activity curves were generated, and the proportion of stroke volume ejected during the different thirds of systole was computed. Peak ejection rate was faster in hyper-

trophic cardiomyopathy ($3.7(0.6)$ ed v/s) than in normal individuals ($3.4(0.4)$ ed v/s, $p < 0.01$) and slowest in aortic stenosis ($3.21(0.4)$ ed v/s, $p < 0.001$). Time to peak ejection rate was shorter in hypertrophic cardiomyopathy ($172(32)$ ms) than in normals ($206(30)$ ms, $p < 0.01$) and longest in patients with aortic stenosis ($218(28)$ ms, $p < 0.01$). Ejection time was prolonged in hypertrophic cardiomyopathy ($394(58)$ ms) and aortic stenosis ($386(33)$ ms) compared with normals ($361(30)$ ms, $p < 0.05$). The proportion of volume ejected in the first third of systole was greater in hypertrophic cardiomyopathy ($39(5)\%$) than in normals ($32(6)\%$, $p < 0.01$) and least in aortic stenosis ($21(4)\%$, $p < 0.001$). The volume ejected during the last third of systole was only 15% in hypertrophic cardiomyopathy compared with 20% in normals ($p < 0.01$) and 30% in aortic stenosis ($p < 0.001$).

This supports the view that gradients in hypertrophic cardiomyopathy do not represent true obstruction to left ventricular emptying and that the haemodynamic significance of gradients of similar magnitude is different in hypertrophic cardiomyopathy and aortic stenosis.

Maximal force, fibre type, and enzymatic activity in quadriceps of patients with severe heart failure: a mechanism for reduced exercise capacity

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The mechanisms limiting exercise capacity in patients with chronic heart failure (CHF) are uncertain but are in part related to underperfusion of skeletal muscle on exercise. We have investigated whether in addition there are changes in maximal force of contraction, fibre type, and enzymatic activity in skeletal muscle. Ten patients (8 men, 2 women) mean age 52 years (range 33–70) with CHF (NYHA class III) were studied. Symptom limited maximal oxygen consumption ($\text{VO}_2 \text{ max}$) was measured during treadmill exercise. Maximal force of isometric contraction of quadriceps muscle was determined. A needle biopsy of the quadriceps muscle was performed under local anaesthesia when the patient was at rest. $\text{VO}_2 \text{ max}$ was 11.7 (range 9–12) ml/kg/min. Maximal force of isometric contraction was reduced to 55 (16)% of the predicted value for weight. There was atrophy predominantly of type II (fast twitch)

muscle fibres in eight of the 10 patients. Muscle capillary density was unaltered. Analysis of mitochondrial enzymatic activity (cytochrome oxidase and succinate reductase) in the muscle sample showed no major abnormality, and changes known to occur in patients with poor skeletal muscle blood flow due to peripheral vascular disease were absent.

Skeletal muscle function and composition is altered in CHF. Loss of muscle bulk and force and alteration of fibre type may make a significant contribution to exercise intolerance in CHF.

Exercise testing six weeks and 18 months after myocardial infarction in patients under 55 years

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Exercise tests at six weeks and 18 months after myocardial infarction were compared in 80 patients under 55 years. Only one patient died during the 18 months. Of the 27 patients with angina at six weeks, 25 (93%) had angina or required coronary artery surgery (CABG) for symptoms by 18 months, compared with 16 (30%) of the 53 patients who did not have angina at six weeks ($p < 0.001$). CABG for severe symptoms was needed in 12 (44%) of the 27 patients with angina at six weeks compared with 5 (9%) of the 53 patients who did not have angina at six weeks ($p < 0.001$). At six weeks the 17 patients who later had CABG had a significantly shorter exercise time (ET) ($10.6(0.8)$ min *vs* $14.6(0.4)$ min; $p < 0.001$) and heart rate $\times$ blood pressure ($\text{HR} \times \text{BP}$) ($17.9(1.0) \times 10^3$ *vs* $22.8(7.3) \times 10^3$; $p < 0.01$) than those who did not. Their ET and $\text{HR} \times \text{BP}$ at 18 months (following their CABG) were significantly increased ($14.8(0.5)$ min; $p < 0.001$; $27.2(1.2) \times 10^3$; $p < 0.001$) and were similar to results in those who did not have operation ($15.2(0.4)$ min; $26.4(1.0) \times 10^3$). The ET and $\text{HR} \times \text{BP}$ of those patients not having CABG did not change significantly between six weeks and 18 months.

Therefore, in patients under 55 years the prognosis after myocardial infarction is good; angina at six weeks is likely to persist and CABG is commonly needed for symptoms. In contrast CABG for symptoms is infrequently needed in patients without angina at six weeks. In most patients the functional outcome after myocardial infarction is predicted by their exercise tolerance at six weeks.

A comparison of exercise testing at ten days and three months after myocardial infarction: relation to the pattern of coronary disease

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Exercise testing may indicate the prognosis and severity of coronary disease in survivors of acute infarction. Not all patients, however, with a positive result on submaximal testing early after infarction have continuing cardiac symptoms, which may be because such patients have a different pattern of coronary disease compared with those whose symptoms persist. Accordingly we studied the coronary anatomy in patients with a positive submaximal exercise test at 10 days after infarction and correlated this with the results of a maximal exercise test at three months. Eighty nine of 169 patients had a positive exercise test at 10 days. Seventy five patients were re-exercised at three months; 39% were positive at the same workload, 32% were positive at higher workloads, and 29% were negative. Five of the remaining 14 patients had died and nine had coronary artery surgery within three months. A score of the severity of coronary disease was higher in patients whose exercise test remained positive (21.8 (8.5), $n=53$) compared with those whose test became negative (15.8 (4.7), $n=22$, $p<0.01$). Significant stenoses in non-infarct related arteries were equally common in patients from both groups, but collaterals were more commonly found in patients whose test remained positive (75% *vs* 45%, $p<0.02$).

Thus 25% of patients with a positive exercise test at 10 days will have a negative test at three months; these patients have less coronary disease (although as many major arteries will be affected) and fewer of them have collaterals.

The Mason-Likar "modified" exercise electrocardiograph: essentially identical to the 12 standard leads?

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The standard 12 lead electrocardiograph cannot be recorded during exercise because of motion artefact and baseline shift. The widely used Mason-Likar torso electrode positions were claimed to produce electrocardiographs "essentially identical" to standard 12 lead recordings, while the precise location of the modified left leg electrode was said not to be critical. We have compared the standard 12 lead electrocardiograph with the Mason-Likar electrocardiograph at rest using four different left leg electrode positions in 29 patients; nine had a normal resting electrocardiograph while 20 had previous infarction (7 anterior, 10 inferior, and 3 inferolateral). Placement of the limb electrodes on to the Mason-Likar torso positions in these patients caused great distortion of the electrocardiograph with a rightward shift of the mean QRS axis, a significant reduction in R wave amplitude in leads I and aVL, and an increase of up to 400% in R wave amplitude in leads II, III, and aVF. R wave amplitude in the chest leads was also altered. Modified electrocardiographs recorded using the different left leg electrode positions were different again from each other. The so-called "inferior" leads on the exercise electrocardiograph appear in fact to be modified inferior/anterior/lateral leads, correlating significantly with R wave amplitude in the anterolateral chest leads. The inferior surface of the heart is therefore not represented in isolation on the exercise electrocardiograph, explaining (a) the inability of the exercise test to predict the location of coronary artery disease, (b) the development of ischaemic changes in the "inferior" as well as the anterior leads in patients with disease limited to the left anterior descending coronary artery, and (c) the high incidence of false negative tests in patients with isolated disease of the right or left circumflex coronary arteries.

The significance of painless ST segment depression assessed by ambulatory pulmonary artery pressure monitoring

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In order to study the significance of painless ST segment depression in patients with coronary artery disease (CAD), we have developed a system for recording ambulatory pulmonary artery pressure using a transducer tipped catheter with simultaneous frequency modulated electrocardiograph (ECG) and

a miniaturised tape recorder. In 17 patients with CAD studied for 650 hours there were 40 episodes of angina recorded during the day. In two episodes of angina the ECG and pulmonary artery diastolic pressure (PADP) did not change. In nine a significant increase in PADP preceded the onset of ST depression, in 10 the reverse occurred, and in the remainder the changes were simultaneous. Peak ST depression and peak PADP occurred simultaneously. ST depression was more prolonged (2.3 min) than the PADP elevation (1.4 min). The increase in PADP on exertion (86%, range 33–237) was greater than that at rest (63%, range 23–128). In these patients 40 episodes of daytime painless ST depression were also recorded. The haemodynamic and ST changes were similar to those seen during painful episodes. The increase in PADP was lower in the painless (67%) than in the painful episodes (86%). Two episodes of PADP rise occurred in the absence of ST changes. In 13 episodes of nocturnal ST depression the changes were similar to daytime episodes except that the rise (50%) in PADP was smaller. Thus, ambulatory pulmonary artery pressure monitoring has shown that painless ST depression differs from painful ST depression only in the magnitude of the haemodynamic response.

Anomalous origin of left coronary artery from pulmonary artery: ligation versus establishment of a two coronary system

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Between 1959 and 1985, 24 patients (mean age 38 months, range 15 days to 13 years) with anomalous origin of the left coronary artery from the pulmonary artery as an isolated lesion had surgical repair at the Children's Hospital, Boston. In 11 cases a left coronary aortic tunnel was created using a pulmonary artery baffle (Takeuchi) with no early or late deaths during a mean follow up of 19 months. Late complications of this procedure included moderate aortic incompetence (one), pulmonary stenosis (two, one required re-operation), obstructed baffle (one asymptomatic). In 11 cases of coronary ligation or ostial closure there was a 27.3% early mortality and 25% late mortality over a mean follow up of 10½ years. Late complications included residual shunt (three, two required re-operation), severe mitral incompetence (one), and recurrence of angina (one). Fifteen patients presented in congestive heart failure (mean age 3.3 months), two had angina (mean age 14

months), and four had asymptomatic murmurs (mean age 8½ years). All deaths both early and late occurred in the group who presented in congestive heart failure and were not revascularised. Five infants who presented with profoundly depressed ventricular function and moderate to severe mitral regurgitation, together with widespread Q waves on the electrocardiogram showed dramatic improvement in ventricular function after the Takeuchi procedure. The Takeuchi procedure is a simple and effective means of establishing a two coronary system in the child with anomalous origin of the left coronary artery. It is particularly recommended over coronary ligation in those presenting with congestive heart failure.

Atrial distension may be a stimulus for the release of atrial natriuretic peptide in children with cardiac diseases

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Cardiocytes of human atria possess specific granules which store a family of polypeptides. The bioactive peptide, termed alpha human atrial natriuretic peptide (ANP), has potent diuretic, natriuretic, and vascular relaxing properties. In experimental animals stretching of the atrial wall is thought to be a stimulus for release of ANP into the circulation. We measured plasma ANP concentrations in children with cardiac diseases that are known to be associated with raised atrial pressure. Thirty two children with various types of congenital heart diseases (age 1 month–17 years) and four children with cor pulmonale (age 17 months–27 months) were studied and compared with a control group. The control group consisted of 51 children (age 6 months–18 years) recovering from diseases unrelated to the cardiopulmonary system and with intact salt and water balance. In the control group there was a narrow and well defined range of plasma ANP concentrations (3–75 pg/mg, mean 45.6) which showed no age dependency. In 21 out of 36 children with cardiac disease, however, plasma ANP concentrations (range 85–967 pg/ml) were greater than the highest ANP concentration in the control group. In patients with a markedly enlarged right atrium such as those with tricuspid atresia (n=3), Ebstein's anomaly (n=1) and cor pulmonale plasma ANP concentrations were up to 10–20 times higher than the mean concentration in control children. In 18 children

there was no significant difference between venous and arterial plasma ANP concentrations. During cardiac catheterisation a supraventricular tachycardia occurred in a 4 year old child with atrial septal defect. Plasma ANP concentrations rapidly increased from 50.4 pg/ml to maximum of over 700 pg/ml during tachycardia and mean atrial pressure increased from 5 to 10 mm Hg. The results of our study accord with the results of experiments in rats and support the hypothesis that ANP release is stimulated by atrial distension.

The management of interrupted aortic arch

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From October 1975 to February 1985, 12 patients with interrupted aortic arch (11 type B and 1 type A) were treated by operation at the Wessex Cardiac Surgical Centre, Southampton. Association lesions included ventricular septal defects (11); uni-ventricular heart (1); aortic valve abnormalities (5); coarctations (2); aberrant right subclavian arteries (2); and one each of right sided aortic arch, truncus arteriosus, double outlet right ventricle, and sub-aortic stenosis. Mean age and weight at operation were 51 days (range 2 days–9 months) and 3.32 kg (range 1.6–7.5 kg) respectively. A one stage primary repair of all lesions was attempted in eight cases (which has been our preference where possible) and repair of the interrupted aortic arch plus pulmonary artery banding in four cases. Early mortality was 25% with a late mortality of 22.2% for hospital survivors. Mean follow up is 37 months. Early mortality was due to low cardiac output with failure to wean from cardiopulmonary bypass (1), subaortic stenosis (1), and truncal valve insufficiency (1). Late mortality was due to failure to wean from cardiopulmonary bypass after repair of anastomotic narrowing (1) and sudden unexplained death (1). Total complications seen in long term follow up included subaortic stenosis (1), aortic stenosis (1), and anastomotic stenoses (3). Two patients had debanding of the pulmonary artery and successful repair of complex lesions 18 days and six months postoperatively. Associated stenotic lesions of the left ventricular outflow tract, both congenital and acquired, are common and may add to the technical problems of operative management and affect long term results.

Lung biopsies in different types of congenital heart disease: computer-assisted structural and functional correlations

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Pulmonary vascular structure was analysed using morphometric techniques in lung biopsy specimens from 90 cases of ventricular septal defect (VSD), 38 cases of complete atrioventricular septal defect (AVSD) without important left atrioventricular valve regurgitation (71% biopsy specimens), and 28 cases of transposition of the great arteries (TGA) with VSD. Cases of VSD showed a significant sustained increase in pulmonary arterial muscularity from age 3 weeks until 10–15 years ($p < 0.0001$), when fibrotic intimal proliferation obstructed the pre-acinar arteries and reduced intra-acinar arterial muscularity. Intimal damage increased with age, mean pulmonary arterial pressure, and resistance ($r = 0.4, 0.6$, and 0.6 respectively; $p < 0.0003$). Intra-acinar arteries were reduced in size in 18% and in number in 23% of cases. Unlike VSD, in AVSD severe intimal proliferation appeared by 6–12 months and was associated with an immediate but gradual reduction in muscularity. Muscularity was inversely related to age and resistance ($r = -0.4$ and -0.6 respectively; $p < 0.001$), without grade IV changes. A logistics regression model predicted the severity of disease with a concordance rate of 82%. In TGA with VSD, unlike VSD or AVSD, muscularity was significantly increased only until 7–9 months when rapidly developing occlusive intimal proliferation produced an abrupt reduction in muscularity of 10–12 months. Thus, each of the common types of congenital cardiac anomalies elicits a different structural response from the pulmonary circulation. The findings help to explain the clinicopathological grey zone preceding classic grade IV changes.

Does epoprostenol (prostacyclin) enhance the selective pulmonary vasodilator effect of oxygen in children with congenital heart disease?

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To assess the reversibility of any elevation in pulmonary vascular resistance we have obtained dose

response curves for the effects of epoprostenol (prostaglandin, PGI_2) on the pulmonary and systemic circulations in 20 children (median age 3 years) with pulmonary hypertension complicating congenital heart disease. Results were obtained with the children breathing both air and 100% oxygen. Remote respiratory mass spectrometry was used to measure oxygen consumption and hence cardiac output by the direct Fick principle, irrespective of the inspired oxygen tension. The dose response curves were analysed using Williams's test. When the subjects breathed air, PGI_2 caused a dose dependent fall in pulmonary vascular resistance (from 11.12 to $8.67 \text{ mm Hg l}^{-1} \text{ min m}^2$) (SED 0.5 , $p < 0.01$). The level of the pulmonary vascular resistance when the subjects breathed air with 20 ng/kg/min PGI_2 being infused was not significantly different from that found when they breathed 100% oxygen (8.67 vs $8.93 \text{ mm Hg l}^{-1} \text{ min m}^2$, SED 0.55). Infusion of PGI_2 while the subjects breathed 100% oxygen caused an additional dose dependent pulmonary vasodilation (8.93 to $7.23 \text{ mm Hg l}^{-1} \text{ min m}^2$, SED 0.3 , $p < 0.01$). An analysis of variance showed that the effects of PGI_2 on the pulmonary vascular resistance were independent of the inspired oxygen tension. Unlike 100% oxygen, PGI_2 was not selective and caused tachycardia and systemic hypotension. These results suggest that in children with congenital heart disease it may be necessary to administer a bloodborne as well as an airborne pulmonary vasodilatory to measure the full extent of reversible pulmonary vasoconstriction when assessing the pulmonary circulation before possible cardiac surgery.

The Doppler evaluation of discrete subvalvar and multilevel outflow tract obstruction in congenital heart disease

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Both continuous wave (CW) and pulsed (PW) Doppler can accurately assess isolated semilunar valve stenosis in children. Little attention, however, has been paid to sub-valve obstruction where type (fixed ventricular septum dynamic), length, and the multilevel nature of the obstruction create more complex problems. To assess Doppler analysis of complex subvalvar obstruction in children, 84 lesions were studied. These were subdivided into

two groups: (a) isolated outflow tract obstruction—subaortic membrane 13, left ventricular tunnel 5, hypertrophic cardiomyopathy (HOCM) 7, right ventricular infundibular stenosis 4, obstructed outlet foramen 11; and (b) multilevel outflow tract obstruction—tetralogy of Fallot 31, complex left ventricular outflow obstruction 9, and subaortic obstruction (univentricular heart) 4. Correlative haemodynamic and angiographic information was available in all. Both CW and PW Doppler identified two discrete wave forms—one fast rising representing fixed subvalve obstruction and the other slow rising and consistently representing dynamic muscular obstruction. Where multilevel obstruction included fixed and dynamic components, both wave forms were superimposed on CW in proportions appropriate to the anatomy. Isolated fixed obstruction occurred in subaortic membranes and in eight of 11 patients with obstructed outlet foramens. Isolated dynamic obstruction was present in all patients with HOCM, isolated right ventricular infundibular obstruction, and in three of 11 with obstructed outlet foramens. Combined fixed and dynamic obstruction was recorded in the remainder. Where superimposed wave forms were recorded the gradient was consistently underestimated.

We conclude that combined CW and PW Doppler determine the nature of subvalve obstruction, accurately reflecting the relative proportions of both dynamic and fixed components. Where only one component is identified peak velocity reflects peak gradient. Where both components are present gradient assessment using the Hatle equation is inaccurate.

How soon after PTCA should its results be assessed by exercise testing?

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In 52 patients following successful percutaneous transluminal coronary angioplasty (PTCA) maximal exercise tests were performed at three days and were compared with a similar test after one month. Twenty three of the patients had a normal electrocardiogram (ECG) and no chest pain in both tests. Fifteen patients had ECG signs of reversible ischaemia but no chest pain at the first test; 10 of these had completely normal ECG findings and no chest pain during effort at the one month test. These 10 patients were the only group to achieve a significantly higher exercise duration at the second test. Twelve patients had ECGs positive for revers-

ible ischaemia and developed angina on exercise in the first test; all of these 12 patients showed the same findings at the one month test and this group had a significantly lower exercise capacity than the remaining patients. Previous myocardial infarction and non-dilated disease in other vessels was significantly more common in the group with positive findings at both tests ($p < 0.001$) and the findings probably reflect disease elsewhere in the heart rather than recurrence of the dilated stenosis. Follow up exercise tests after six months showed closer agreement with the results at four weeks than with those at three days, and the three day test did not help to identify patients who subsequently relapsed.

We conclude that during the first few days after PTCA false positive exercise tests may occur in 20% of patients. Assessment of exercise testing four weeks after the procedure avoids this problem.

Coronary artery thrombus as a risk factor for acute vessel occlusion during percutaneous transluminal coronary angioplasty: improving results

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During an early percutaneous transluminal coronary angioplasty experience, from October 1979 through March 1983, we reported that pre-existent coronary artery thrombus was associated with a significant increase in the incidence of acute coronary occlusion during angioplasty. Thus complete occlusion occurred in 11 (73%) of 15 patients with thrombus undergoing angioplasty compared with 18 (8%) of 233 without thrombus ($p < 0.001$). To study the effect of improved technology (steerable guiding systems) and dilatation strategy (full intravenous heparinisation for 24 hours following the procedure and more intensive use of antiplatelet medications) angiograms from 297 consecutive patients without evidence of acute myocardial infarction who underwent angioplasty from April 1983 through March 1985 were reviewed. Pre-existent coronary artery thrombus was present in 34 (10%) patients of whom eight (24%) developed complete occlusion during or immediately after the procedure. In the 263 patients without coronary thrombus, acute coronary occlusion occurred in 34 (13%) (24% *vs* 13%, $p = 0.17$). Thus in a more recent experience, patients

with pre-existent coronary artery thrombus are at somewhat greater risk of complete occlusion than are patients without thrombus, but the magnitude of this risk has declined substantially.

The effects of early PTCA on the clinical course of unstable angina

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The medical management of unstable angina is associated with a high incidence of recurrent symptoms and does not prevent myocardial infarction or death in up to 30% of cases during early follow up. We have undertaken early percutaneous transluminal coronary angioplasty (PTCA) in 50 patients with unstable angina in an attempt to improve the clinical course. In each case diagnostic angiography demonstrated a critical proximal stenosis in a major vessel and in 33 patients this was the only lesion. The stenosis was crossed by the PTCA catheter in 76% of cases and successful dilatation was achieved in 95% of these. Angiographic success was reflected by a non-ischaemic predischARGE stress test and correction of symptoms in 75% and 89% of cases respectively. The combined in hospital incidence of myocardial infarction and death was 12%, but it was only 3% in patients with single vessel disease. At six months follow up 77% of patients who had undergone successful PTCA remained symptom free, though repeat procedures had been necessary in 21%. The combined incidence of myocardial infarction and death during follow up was low (8%). These data indicate that PTCA may be undertaken with relative safety in patients with unstable angina and that it leads to a substantial improvement in symptoms that is sustained during early follow up. The benefits of this therapeutic approach may be particularly pronounced in patients with only single vessel disease.

Percutaneous transluminal coronary angioplasty—results in patients with multiple coronary stenoses

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Percutaneous transluminal coronary angioplasty (PTCA) is an acceptable treatment for proximal discrete single vessel coronary disease. The place of PTCA in the management of patients with multiple coronary lesions is less certain. In our first 95 consecutive patients (81 men and 14 women, mean age 58 years) undergoing multi-lesion PTCA 22 patients had multiple lesions in single vessel disease, 49 double, 23 triple, and one left main coronary artery. PTCA was attempted on 213 lesions—115 in the anterior descending or diagonal arteries, 36 in circumflex, and 62 in right coronary arteries. Up to seven lesions in any one individual have been dilated. Primary success, reduction in stenosis without associated acute myocardial infarction or emergency coronary bypass grafting (ECBG), was achieved in 191 (90%) of these lesions. Seventy nine patients (83%) were rendered symptom free. Five (5%) had an associated myocardial infarction. Six (6%) required ECBG and one of these patients died after surgery. Five of the six patients requiring ECBG had PTCA related occlusion in a vessel with compromised or absent collateral supply. In a follow up of 3–24 months 13 patients (16% of primary success group) developed recurrence of angina and 10 underwent repeat PTCA; in eight the second procedure was entirely successful, one required ECBG, and in one a second recurrence lead to referral for elective bypass surgery. PTCA risk relates to operator experience and the presence of established coronary occlusion rather than to the number of lesions or morphology in an individual stenosis.

PTCA is a successful alternative to coronary bypass grafting in a large proportion of patients with multiple lesion, multiple vessel coronary disease. Improvement in long term management or prognosis in such patients remains to be demonstrated conclusively.

Prevention of regional myocardial ischaemia during PTCA—the effects of infusing arterial blood

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Much of the potential risk of percutaneous transluminal coronary angioplasty (PTCA) relates to severe myocardial ischaemia during periods of balloon inflation. We have investigated a new technique for reducing ischaemia by infusing arterial blood through the angioplasty catheter into the distal coronary artery during 60 second dilatations. Symptoms

and electrocardiographic and echocardiographic indices of regional ischaemia were monitored during dilatations with and without blood infusion. The effect of infusing Hartman's solution was also evaluated to control for washout effects. Ten patients were studied. Dilatations without blood produced chest pain after 22.7 (10.2) s (mean (SD)) in seven patients and signs of regional ischaemia in every case; echocardiographic dyskinesia occurred within 16.0 (3.2) s and ST segment elevation (1.9 (1.3) mm) within 18.4 (6.6) s. Blood infusion (45.6 (13.4) ml/min) dramatically reduced manifestations of ischaemia; only one patient experienced pain and dyskinesia after 45 s and 49 s respectively, though ST segment elevation was observed in three cases after 29.3 (5.1) s. The peak ST change, however, was only 0.8 (0.3) mm. In two patients severe chest pain and ST segment elevation were reversed by infusion of blood. Importantly, infusion of Hartman's solution was unhelpful, indicating that delivery of oxygen and not washout of metabolites was responsible for the beneficial effects of blood infusion. These data suggest that the development of PTCA catheter systems which permit blood infusion into the distal coronary artery will improve the safety of the technique. Moreover, by allowing more prolonged periods of balloon inflation a higher success rate can be expected.

Argon laser recanalisation of acutely thrombosed coronary arteries in live dogs

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To assess the feasibility of currently available techniques, in vivo laser recanalisation of acutely thrombosed coronary arteries was attempted using an argon laser delivered in a continuous wave form. Ten anaesthetised mongrel dogs weighing 25–30 kg had their left anterior descending artery thrombosed by passing a low grade current through a guidewire positioned in its proximal end. In six dogs a 140 μ m core optical fibre was then positioned proximal to the thrombus and laser delivery was performed during fibre advancement. Recanalisation was seen in one dog, perforation in four dogs, and neither recanalisation nor perforation was evident in one dog. In the remaining four dogs, a 0.014 inch steerable guidewire was advanced beyond the thrombus and a 3F catheter was advanced over it and positioned distally. After mechanical recanalisation was excluded a 200 μ m core optical fibre was fed through

the 3F catheter and laser delivery was performed during fibre withdrawal across the thrombus. Using this method mechanical recanalisation occurred in one dog and perforation was seen in three dogs.

Argon laser recanalisation of acutely thrombosed coronary arteries in live dogs is feasible but at present results in a high frequency of perforation. This animal model can be used for the development and evaluation of safer systems in *in vivo* laser coronary revascularisation.

Epoprostenol (prostacyclin) therapy during cardiac surgery—is it beneficial?

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Platelet activation with subsequent formation of microaggregates is now known to be a feature of cardiac surgical procedures utilising cardiopulmonary (CPB). Controversy exists in relation to the possible therapeutic role of epoprostenol (prostacyclin, PGI_2) in inhibiting platelet aggregation. The potential benefits have been offset by fears related to severe hypotension experienced in some studies. In a series of experimental animal studies using a prostacyclin dosage protocol of 10 ng/kg/minute for 30 minutes before CPB and 20 ng/kg/minute during CPB the following effects have been observed: (a) preservation of platelet numbers during CPB ($p < 0.01$ vs controls, $n = 16$); (b) significant reduction in platelet aggregation during CPB ($p < 0.01$, $n = 16$); (c) significant reduction in plasma histamine concentrations during CPB ($p < 0.05$, $n = 10$); and (d) insignificant hypotensive effect at normal levels of peripheral vascular resistance ($n = 16$). These results suggest that prostacyclin treatment may have beneficial effects in inhibiting platelet aggregation during CPB and that further clinical studies should now be carried out.

Surgical treatment of absent pulmonary valve syndrome

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The absent pulmonary valve syndrome includes agenesis of the pulmonary valve, annular stenosis, and pulmonary insufficiency. The pulmonary arteries are aneurysmal and usually compress the tracheobronchial tree. These features are associated with a ventricular septal defect and right ventricular hypertrophy. Twenty three patients aged 5 days to 11 years were treated between 1976–1985. Eleven were younger than 1 year. Intractable respiratory syndromes and heart failure were the main feature in the infant group, five required preoperative assisted ventilation. All the children presented with decreased exercise tolerance and repeated respiratory infections. Surgical repair included a closure of the ventricular septal defect in all cases and various techniques of reconstruction of the right ventricular outflow tract. This included a patch enlargement with or without insertion of a xenograft valve and a Dacron xenograft conduit between the right ventricle and pulmonary artery. In the recent years the repair has consisted in an extensive resection of the main pulmonary artery and of the anterior aspect of both the right and left pulmonary arteries with the interposition of an aortic homograft between the right ventricle and pulmonary artery. All 12 patients operated after the age of 1 year survived though some of them are awaiting surgery for replacement of calcified xenograft valves. The superiority of the current technique is better demonstrated in the infant group as all five infants operated in the early years and all six infants operated with our current technique survived. Closure of the ventricular septal defect, reduction of the size of the pulmonary arteries, and insertion of an aortic homograft therefore appears to be the treatment of choice for this difficult malformation.

Long term evaluation of isolated Starr-Edwards aortic valve replacement

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We identified 352 patients discharged from hospital during 1974–1983 who had isolated Starr-Edwards aortic valve replacement with models 1260 and 2400. We followed up 327 (92.8%) patients for up to 10 years, a total of 1616 patient-years, to determine the long term performance characteristics of these prostheses. At operation the mean age of patients was 52.1 (range 14–78) years, 73% were male, and 89% were in sinus rhythm. The aortic valve disease was rheumatic in 75 (23%), congenital in 111 (34%), degenerative in 101 (31%), and associated with

endocarditis in 35 (11%) patients. Total 10 year mortality was 47 deaths (14.4%; 2.9% per patient-year), of which 27 (8.2%) were cardiac in origin with three cases (0.9%) directly valve related due to thromboembolism. Total ten year valve related morbidity in 60 patients (18.3%; 3.7% per patient-year) was due to thromboembolism in 22 (6.7%), prosthetic endocarditis in 14 (4.3%), anticoagulant related haemorrhage in 12 (3.7%), paraprosthetic regurgitation in nine (2.8%), and haemolysis in three (0.9%). Re-operation was performed in 24 patients (7.3%) because of thromboembolism (9 patients, 2.8%), prosthetic endocarditis (8 patients, 2.4%) or paraprosthetic regurgitation (7 patients, 2.1%); all but one re-operation was necessary within the first year after operation. No cases of mechanical valve failure were recorded. Total ten year actuarial estimates of survival were 0.61 (0.066) and freedom from valve related morbidity 0.45 (0.071) (means (SE)).

The Starr-Edwards models 1260 and 2400 aortic valve prostheses show excellent durability without any mechanical failure over a 10 year period. The long term outcome of isolated aortic valve replacement with these models is associated with a low frequency of valve related complications.

Heart-lung transplantation for Eisenmenger's syndrome

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Between May 1981 and January 1985, 13 combined heart-lung transplants were performed in 12 patients for the treatment of end stage Eisenmenger's syndrome. Five patients had had previous intrathoracic operations. There were four hospital deaths: one at operation; and one each at 4, 10, and 33 days after transplantation. Early symptomatic results and cardiopulmonary function were excellent in all operative survivors. Two late deaths occurred at 14 and 15 months after transplantation from accelerated graft arteriosclerosis and respiratory failure respectively. Six patients are alive 12-49 months after transplantation. Six of the eight operative survivors developed major pulmonary complications associated with progressive obstructive airway physiology and obliterative bronchiolitis that were demonstrated on histological examination. Because of this late pulmonary deterioration overall prognosis remains uncertain, and may limit the value of heart-lung transplantation for Eisenmenger's syndrome.

Cerebral consequences of coronary artery surgery

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A prospective multidisciplinary controlled study of the cerebral consequences of coronary artery bypass surgery is being undertaken. Patients undergoing coronary artery surgery by a standard protocol have preoperative digital subtraction angiography (DSA) of the head and neck vessels, regional cerebral blood flow measurements, and neurological, neuropsychological, and psychiatric examinations. These are repeated, excluding DSA, at eight days and eight weeks postoperatively. A control group of major vascular cases and thoracotomies is also being studied. Besides accurately quantifying the incidence of central nervous system complications, the results of the assessments are compared with the state of the head and neck vasculature, regional cerebral blood flow changes, and details of the bypass and postoperative management. To date, results have been analysed in 55 patients in the coronary surgery group. Focal neurological changes were found in one patient at eight days and no patient at eight weeks. Significant neuropsychological deficit was found in 95% of patients at eight days and 33% at eight weeks, most markedly in verbal memory, visual perception, and concentration. Mean cerebral blood flow was significantly reduced at eight days ($p < 0.02$) and at eight weeks ($p < 0.05$). The greatest reduction in neuropsychological performance and cerebral blood flow was found in those patients with the longest bypass times or with major postoperative complications. In the control group no neurological deficit has been found, the mean cerebral blood flow was increased at both eight days and eight weeks, and a significant neuropsychological deficit was found in 87% of patients at eight days but in no patients at eight weeks.

Comparison of bioprosthesis degeneration in the aortic versus the mitral position

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Cross section echocardiography was performed 40 (17) months (mean (SD)) after operation in 45

patients aged 22 (5) years with rheumatic heart disease in whom simultaneous aortic and mitral porcine bioprosthetic valve replacement had been performed. The echocardiographic and morphological features of 23 bioprosthetic valve explants from 21 patients subjected to re-operation were compared. The following associates were found—normal cusp mobility on echocardiography with echoes ≤ 3 mm thick (stage I) indicated cusp fibrosis with or without retraction; normal cusp mobility with echoes ≥ 3 mm thick (stage II) indicated focal cusp calcification; restricted cusp motion with bright echoes > 3 mm thick (stage III) indicated extensive calcification and reduced cusp mobility; and a prolapsing cusp (stage IV) identified a torn calcified cusp. Using these associations the following subgroups were identified. Forty one patients had aortic stage I disease of whom 25 had mitral stage I, nine stage II, five stage III, and two stage IV disease. Two patients with aortic stage II disease had mitral stage I disease, and only one patient had aortic stage III disease with mitral stage I disease. One patient had aortic and mitral disease both stage III. In young patients with rheumatic heart disease porcine bioprosthetic valves degenerate very early, particularly when placed in the mitral position.

Doppler ultrasound assessment of 155 patients with investigational bioprosthetic valve replacement

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Having previously established the validity of Doppler ultrasound examination in assessing bioprosthetic valve function, we applied the technique to 155 patients with the newer bioprostheses (62 Wessex porcine (W), 34 low profile Ionescu-Shiley (IS), and 45 Hancock pericardial (HP)). Doppler examination was performed using a Vingmed Alfred Velocimeter with a 2 MHz transducer interfaced to a spectrum analyser. Valve gradients were calculated from the continuous wave mode using the modified Bernoulli equation. Prosthetic regurgitation was assessed by both continuous and pulsed wave Doppler examinations. Cross sectional echocardiography was performed in all patients and failed to show any structural abnormalities. Mean mitral gradients in the competent bioprostheses were significantly lower in the IS type (3.03 (0.8) mm Hg) than in the W type (3.52 (0.9) mm Hg) ($p < 0.02$) and

HP type (3.65 (1.2) mm Hg) ($p < 0.05$); and mitral pressure half-times were longer in the HP type (97 (33) ms) than in the W type (80 (21) ms) ($p < 0.02$) and IS type (80 (24) ms) ($p < 0.05$). There was no significant difference in the peak aortic gradients (W, 17.9 (8.3) mm Hg; IS, 17.1 (6.0) mm Hg; HP, 15.1 (5.7) mm Hg). Regurgitation was detected in 11 mitral (2 of 41 W, 5 of 25 IS, 4 of 25 HP) and 11 aortic bioprostheses (5 of 20 W, 3 of 15 IS, 3 of 27 HP).

In conclusion, Doppler ultrasound examination is of value in assessing valve gradients in bioprosthetic valves and can detect valve regurgitation at an early stage in these patients.

Severe left main stem stenosis: safety of discharge home to await elective surgery

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Seventy one patients with a severe stenosis of the main stem of the left coronary artery were identified at first coronary arteriography in the period 1979–July 1984. Of these, 11 patients were kept in for operation (mostly because of unstable angina) five died in hospital, and twelve cases were deemed to be inoperable because of either poor left ventricular function or diffuse disease of the distal coronary vessels. Forty three patients with stable angina were allowed home to await elective operation. No patient died of a cardiac cause while waiting; one patient died of a cerebral haemorrhage after three months' wait. Two patients were re-admitted with unstable angina without evidence of infarction after six weeks and three months; both went on to have operation during the same admission. When re-admitted for operation, ten patients thought that their angina had worsened, four that it had improved, and the remainder were unchanged.

Discharge home of patients with stable angina and a severe stenosis of the main stem of the left coronary artery to await elective surgery is broadly a safe policy.

Clinical budgeting in cardiology and cardiac surgery

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The introduction of new management structures and

of clinical budgeting into a District suffering reductions of revenue was recognised as an important development for regionally funded specialties such as cardiology and cardiac surgery. Accurate identification of true costs would allow direct discussions with the Regional Health Authority and reduce potential conflicts with professional colleagues. In 1984/5 in a combined regional cardiology and cardiothoracic surgery unit of 58 beds, a budget of £3.8 million was identified. The unit undertook approximately 800 cardiac catheterisations, 700 cardiac surgical procedures, and 300 pacemaker implantations. Direct costs such as staff costs (£1.5 million) and medical equipment costs (£1.08 million) were easy to identify. Other costs, however, such as those in other departments—for example radiology, pharmacy, and pathology were not easy to identify and arbitrary charges made may not reflect true costs. Indirect costs such as estate management and domestic and portering services were calculated on the basis of bed-days occupied as a percentage of total hospital bed-days. The advantages of such a clinical budget include (a) separate identification of a regional specialty costs within an overall hospital budget, reducing the element of competition with other specialties; (b) flexibility in use of resources with an ability to implement changes more rapidly; (c) savings implemented are of direct benefit to the user; (d) awareness of costs of individual procedures allows consideration of alternatives.

A moderate amount of professional time has been required to set up and refine the clinical budget and less is required to review it. The advantages outweigh the disadvantages.

Arrhythmia in children and adolescents with hypertrophic cardiomyopathy: incidence and relation to prognosis

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Annual mortality from sudden death is approximately 5% in children and adolescents with hypertrophic cardiomyopathy. Clinical, electrocardiographic, and haemodynamic characterisation does not identify those who are at particular risk. To determine the incidence and relation of arrhythmia to prognosis we have performed prospective 48 hour electrocardiographic monitoring in 36 consecutive

patients with hypertrophic cardiomyopathy: three were infants (<1 year), 17 were 1–14, and 16 were 15–21 years of age. On the initial 48 hour electrocardiographic monitoring all were in sinus rhythm, none had ventricular tachycardia, one had more than 250 ventricular extrasystoles per day, three had episodes of supraventricular tachycardia and another had re-entry atrioventricular tachycardia associated with overt pre-excitation. The patients were followed 1–6 years (median 2) from the initial 48 hours electrocardiogram. In 12 patients, 23 additional 48 hour electrocardiograms were performed: two had ventricular tachycardia, one developed atrial fibrillation but no other new arrhythmias were detected. Twenty eight received beta blockers, two had verapamil, and the child with the Wolff-Parkinson-White syndrome had amiodarone. Four patients died suddenly, another was resuscitated from out of hospital ventricular fibrillation, and the only child to undergo myectomy died post-operatively. None of the patients who died had arrhythmias during 1–7 days (mean 3) of electrocardiographic monitoring. In contrast to adults arrhythmias are uncommon in children and adolescents with hypertrophic cardiomyopathy and are not a marker of those at particular risk of sudden death. This suggests that in children with hypertrophic cardiomyopathy the initiating event of sudden death is more likely to be an acute haemodynamic alteration than an arrhythmia.

Multi-programmable pacemakers—essential for pacing in children

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Twenty seven of 30 children (mean age 7.5 years) who received a permanent pacemaker since 1979 had multi-programmable pacemakers (Siemens 668 in eight, Siemens 674 in two, Cordis 340A in seven, Biotronic Neos in seven, Medtronic Activitrix in one, and Teletronics Optima in one). Indications of pacing were complete heart block (CHB) in 20, sinus node dysfunction (SSS) in six, prophylaxis in one, and control of refractory tachycardia in three. Programmable variables were used to reduce voltage output or pulse duration in nine children with low chronic stimulation thresholds (seven endocardial, two epicardial) to increase battery longevity. To identify pacemaker-dependent patients, underlying

heart rhythm in 20 children with CHB was assessed by programmed gradual reduction of the pacemaker rate. A stable escape rhythm (range 35–70 beats per minute) was found in 16, but in four children there was no endogenous activity and symptoms of pre-syncope occurred at 30 beats per minute. In four children with a late threshold rise increase in voltage (3) or current output (1) restored effective pacing before lead replacement in three and obviated re-operation in one. Re-operation was prevented in one child with sensing failure 1 month after implant by increasing the programmable sensitivity. Rate-programmability permitted higher more physiological heart rates of 90–100 beats per minute in four infants (mean age 0.6 years) and in six children less than 5 years old with CHB. In one child heart failure responded solely to an increase in pacing rate from 80–100 beats per minute. All six patients with SSS had low standby rates programmed (mean 50 beats per minute) to allow as much sinus rhythm as possible without symptoms. Multi-programmable pacemakers are invaluable in the paediatric age group.

Assessment of pulmonary vascular resistance in patients with ventricular septal defect

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Pulmonary vascular resistance index (PVRI) was measured at rest and with an infusion of isoprenaline (usually 0.05 to 0.1 $\mu\text{m/kg/min}$) in 31 patients with ventricular septal defect and pulmonary vascular disease. Patients were divided into group A or B according to whether or not PVRI fell to 7 units. m^2 with isoprenaline: group A (responsive), $n=15$, age 0.3–14 years (median 2), PVRI resting 8–15 (median 9.0), PVRI isoprenaline 1.9–6.6 (median 4.2); group B (non-responsive), $n=16$, age 1.32 years (median 2), PVRI resting 8–43 (median 18), PVRI isoprenaline 9.3–35 (median 16). Other variables, including resistance ratios, showed less clear discrimination. For example, 4/13 patients in group A had resting pulmonary: systemic resistance ratios >0.5 , and 4/16 patients in group B had resistance ratios <0.5 . Fifteen group A patients underwent operation. One patient died at one month (grade 1 Heath-Edwards changes), one showed progressive

pulmonary vascular disease after a breakdown of the repair, and the remainder have done well. In nine patients undergoing postoperative restudy the highest PVRI at rest was 5.2 units. m^2 and with isoprenaline 2.7 units. m^2 . Operation was undertaken in 3/16 group B patients, with two deaths (grade 4 Heath-Edwards changes); the third showed progressive pulmonary vascular disease. All non-operated group B patients showed progression of pulmonary vascular disease with one death (grade 6 Heath-Edwards changes).

Reduction of PVRI to 7 units. m^2 with isoprenaline predicts a good pulmonary vascular response to operation irrespective of resting PVRI. Operation is probably contraindicated unless this level can be achieved.

Transposition of the great arteries—adults and adolescents late after Mustard procedure

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Fourteen patients with transposition of the great arteries aged 15–26 years treated by Mustard procedures at the age of 14 months to 14 years were evaluated with Holter monitoring, ventricular function assessment, and treadmill exercise studies as well as clinical examination. Ten had had earlier atrial septectomy (Blalock-Hanlon) when aged 9 days to 6 years. One died with chronic failure and unstable atrial arrhythmias aged 15 years in a disco, and one has been lost to follow up. Six of the remaining 12 have basic sinus rhythm and the rest have nodal rhythm or atrial flutter with paced block. Electrocardiographic monitoring shows changing arrhythmias such as flutter, supraventricular tachycardia, sinus arrest, bigeminy, and nodal rhythm in 11; these are symptomatic in five. One patient with left outflow obstruction was resuscitated from “death” probably from rapid atrial tachycardia. One other has severe left ventricular outflow obstruction. Three require diuretics for impaired right ventricular function and three have tricuspid regurgitation. Ten survivors lead normal lives and two have mild disability. One uncomplicated pregnancy with a normal baby has occurred. After good surgery, provided there is regular assessment and control of arrhythmias and failure, this group of patients once doomed to die in infancy live good lives in the third decade.

Success and complication rates for coronary angioplasty in patients with and without previous myocardial infarction

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In 116 consecutive patients undergoing coronary angioplasty for the first time 49 (group 1) had previously documented myocardial infarction. In group 1 the primary success rate was 57% compared with 85% in 67 patients (group 2) without previous infarction. There was no difference in the age, sex, site of lesion, or severity of stenosis between the two groups. Failure in group 1 was due to failure to cross in eight cases, failure to dilate in two, myocardial infarction in four, and emergency coronary artery bypass grafting in four with one death. Failure in group 2 was due to inability to cross in eight and myocardial infarction in two with no emergency surgery or death. Acute coronary occlusion occurred in six patients in each group and was managed by immediate repeat angioplasty in all. In group 1 this was associated with myocardial infarction in each instance, while in group 2 repeat angioplasty was successful in all six but two patients sustained non-transmural infarction.

In this series of patients undergoing percutaneous transluminal coronary angioplasty in one centre the lower success rate in patients with previous myocardial infarction was primarily due to the increased incidence and severity of complications rather than to failure to cross the lesion.

Emergency surgery following percutaneous transluminal coronary angioplasty

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In the three year period from August 1982 to July 1985, 211 percutaneous transluminal coronary angioplasties were carried out in two cardiological units, with 10 patients (4.7%) being referred for emergency surgery. There were seven men and three women with an average age of 55 years (40–65). Nine of the patients were originally admitted with acute myocardial ischaemia, two with definite myocardial infarctions. All ten patients underwent single vessel angioplasty, six to the right coronary artery and four to the left anterior descending coronary artery. In

one patient a broken guidewire impacted in the left anterior descending coronary artery (without ischaemic changes) was the cause of referral for emergency surgery. The other nine had evidence of prolonged acute ischaemia precipitated by total obstruction of the vessel by dissection (5 patients), thrombus (2 patients), or irreversible spasm (2 patients). Single coronary artery bypass grafts were performed in seven patients, double grafts in two, and one patient had a triple bypass. The average revascularisation time (from onset of ischaemia to completion of graft) was 290 minutes (range 210–380). One patient required intra-aortic balloon pump support postoperatively. There were no operative deaths. Although six patients had a significant rise of myocardial specific creatine kinase, in only three was there accompanying electrocardiographic evidence of transmural infarction. The patient with the broken guidewire which was not completely removed was re-admitted three months postoperatively with an anterior myocardial infarction.

Acute and chronic angiographic effects of in vivo coronary laser angioplasty

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The fiberoptic transluminal delivery of laser energy may provide the possibility of improving the primary success rate of, and perhaps of widening the indications for, coronary angioplasty. Potential dangers of laser angioplasty can be early (acute perforation) or late (stenosis or aneurysm). To find the acute in vivo perforation threshold of arteries of similar size to the proximal human coronary arteries, we delivered 30 separate argon laser pulses of different energies transilluminaally to separate sites in normal rabbit iliac and canine coronary arteries via a 100 μ m core optical fibre, with fibre tip in contact with arterial luminal surface. Laser perforation occurred in 0/1 at 0.2 J, 0/2 at 0.5 J, 0/8 at 1 J, 0/5 at 2 J, 0/6 at 3 J, 4/5 at 4 J, 2/2 at 5 J, and 1/1 at 7 J. To find the coaxial energy threshold for causing early or late angiographic abnormalities, argon laser energy was delivered to the coronary circulation of 10 normal closed chest dogs via a 100 μ m core fibre within a balloon angioplasty catheter, sited by a guide catheter under x ray screening. Three laser pulses (1, 2, and 3 J) were delivered coaxially (balloon inflated) at the

same site. Coronary angiograms were recorded pre-laser, immediately post-laser, and again at 1 week. In three dogs, 5 J coaxial pulses were given in vivo to the other coronary artery. There were seven one-week survivors, all with normal repeat angiograms, three of which had had x ray evidence of pre-laser mechanical perforation. There were two anaesthetic deaths, and two (immediately fatal) laser perforations, one at 3 J (subsequently found to have been non-coaxial), and one after 2×5 J.

Thus (a) coaxial energy of up to 3 J (single pulse or 6 J (cumulative dose) gives no immediate or 1 week angiographic abnormalities; (b) immediate laser perforation is caused by coaxial energy of 10 J (cumulative dose) but not by 5 J; (c) acute mechanical perforation with a 100 μ m fibre lacks the mortality of laser perforation; and (d) the acute in vivo perforation threshold of 2–4 mm diameter arteries (fibre tip in contact with luminal surface) is between 3 J and 4 J.

Which ultraviolet laser wavelengths are selective for atheromatous as opposed to normal arterial wall?

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The immediate danger of laser angioplasty, vessel perforation, is related to the extent of thermal damage suffered by the residual non-vaporised arterial wall immediately subjacent to the laser crater. Pulsed ultraviolet excimer lasers which destroy tissue by photo-ablation (a non-thermal mechanism of molecular disruption) do not cause this region of surrounding thermal damage and thus their use may reduce the risk of vessel perforation. To find which ultraviolet wavelength would be appropriate for the photo-ablation of atheroma we quantified the effect of different energy densities of an excimer laser run at three different wavelengths (193 nm (ArF), 249 nm (KrF), and 351 nm (XeF)) on samples of normal and of atheromatous human postmortem aortic wall in which craters were produced by delivering a train of 250, 20 ns pulses of the directly focused beam at a repetition rate of 2.5 Hz. The range of energy densities used per crater were as follows: 55.5 J/cm² to 277 J/cm² at both 193 nm and 249 nm, and 101 J/cm² to 555 J/cm² at 351 nm. Five different power densities were used at 193 nm and at

249 nm, and four power densities at 351 nm. For each wavelength and at each power density at least five craters were made. A careful record was kept of the energy variables used to produce each crater and their depths were then measured to the nearest 10 μ m. With all three wavelengths crater depth was proportional to both energy density and total energy per crater. This dose response relation was least steep at 351 nm (15 μ m of penetration per J of energy delivered), steeper at 193 nm (66 μ m/J), and steepest at 249 nm, which at each energy density consistently gave greater penetration into atheromatous tissue than it did into normal tissue (144 μ m/J and 124 μ m/J respectively). Such an atheroma-selective effect was not seen at 193 nm or 351 nm.

Thus of the three wavelengths, 249 nm (KrF) appears appropriate for laser angioplasty, and is the pulsed excimer laser wavelength for which a fibreoptic intracoronary delivery system should be developed.

Linoleic acid, leucocyte sodium transport, free calcium, and blood pressure

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Abnormal plasma membrane handling of sodium has been reported in patients with essential hypertension. This has been attributed to genetic alterations of membrane physicochemical structure. In view of reports of a blood pressure lowering effect of polyunsaturated fats, it was decided to investigate whether changes in dietary fat would alter both membrane sodium transport in leucocytes and blood pressure. Twenty two normotensive subjects with no family history of hypertension received either 4 g safflower seed oil (containing 72% linoleic acid) or placebo capsules by random allocation for four weeks. Leucocyte sodium transport studies and free calcium estimations were performed at the end of each dietary period. Membrane lipids were estimated by gas liquid chromatography and blood pressure was measured by a random zero sphygmomanometer. Membrane linoleic acid was significantly increased by safflower seed oil compared with placebo (17 (0.28) vs 16.3 (0.34)% of total lipids, $p < 0.01$). There was a significant increase in sodium pump rate on safflower oil compared with placebo (100 (9.3) vs 72 (5.1) mmol/kg/h, $p < 0.01$). Mean weight, plasma renin activity, and urinary sodium excretion (134 (12.9) vs 139 (10.4) mmol Na⁺/24 h) were unchanged. Systolic blood pressure

fell significantly on safflower oil (125 (3) *vs* 129 (3.3) mm Hg, $p < 0.01$). In 13 subjects leucocyte free calcium was estimated using the fluorescent dye Quin-2. Intracellular free calcium fell on safflower seed oil compared with placebo (110 (5.2) *vs* 133 (9.9) nmol/l, $p < 0.05$).

These results suggest that an increase in dietary polyunsaturated fat can influence sodium pump activity and intracellular free calcium and lower blood pressure by altering the physicochemical properties of the plasma membrane.

Prostacyclin production in saphenous vein from patients receiving aspirin

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Since work showing that daily administration of 300 mg of aspirin approximately halved the risk of subsequent myocardial infarction or coronary death we have noted a large increase in the numbers of patients presenting for coronary artery bypass surgery who have received chronic aspirin therapy. Segments of long saphenous vein (1 cm long) taken at operation from the lower portion of the leg were rested three times for 10 minutes each at 23° in 1 ml of a buffer (132 mmol/l sodium chloride, 5.3 mmol/l potassium chloride, 1.3 mmol/l magnesium sulphate, 1.4 mmol/l calcium chloride, 13.5 mmol/l sodium bicarbonate, 135 mmol/l Hepes/sodium hydroxide, pH 7.4 equilibrated with oxygen:carbon dioxide (95:5 v/v). Vein was then sliced into three weighed rings and prostaglandin production from endogenous substances was then stimulated by vortex mixing each ring for 15 s at 23°C in 0.3 ml of buffer. Prostaglandin production proceeded for a further 2 minutes 45 s where upon the vein was removed and indomethacin (33.3 µg/ml) was added to the buffer. After resting the buffer for 60 min at 23°C the concentration of 6-keto-prostaglandin $F_{1\alpha}$ was measured by radioimmunoassay. Mean venous prostacyclin production was 1.0 (0.8) pg/min per mg wet weight in 10 patients treated with aspirin compared with 13 (8) pg/min per mg in 49 other patients ($p < 0.001$). Postoperative blood loss (measured by total chest drainage) was 798 (65) ml in patients receiving aspirin and 670 (26) ml in other patients ($p < 0.05$).

We conclude that popular current treatment regimens have a very substantial inhibitory effect on venous prostacyclin production and thereby disable one of the main antithrombotic defences of the vessel wall. This is likely to exacerbate platelet activation resulting from damage to the vein graft endothelium

during intra-operative surgical manipulation and hence promote both early and late graft thrombotic occlusion.

Intramyocardial platelet emboli in unstable angina and sudden ischaemic death

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A specific search for platelet emboli in the myocardium was made in 90 patients who had died suddenly (symptoms < 6 hours) of ischaemic heart disease and who had not sought medical treatment in the last two weeks. Cases were divided into those who had complained to their relatives of any new episodic symptoms of chest pain in the week preceding the final event and those who had not. Complaints of vague ill health, tiredness, or indigestion without specifying chest pain were ignored. Platelet emboli were found overall in 27 (30%) of the 90. Emboli were found in 44% of the 36 cases with preceding episodic pain and in only 20.4% of the 54 cases without. The difference is significant ($p < 0.05$) using the χ^2 test corrected for continuity. With one exception platelet emboli were in the myocardium downstream of an atheromatous plaque undergoing rupture or fissuring. The data confirms that platelet embolisation into the myocardium occurs in a proportion of patients who have plaque fissures with exposed mural thrombus. Such pathological studies probably underestimate the true clinical incidence. The association of platelet emboli with what would have been called unstable angina had the patients sought medical help suggests that the episodes of pain may have been mediated by transient ischaemic episodes due to the emboli.

The analogy that has been made between unstable angina and transient cerebral ischaemic attacks known to be due to platelet embolism from ulcerated atheroma in the carotid arteries is confirmed by our study.

Is early recanalisation in acute myocardial infarction recommendable?

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Evidence is finally accruing that myocardial infarct size can be limited, left ventricular function maintained, and early, as well as late, mortality rates halved provided attempts at recanalisation are made within the first few hours after onset of clinical signs and symptoms of artery thrombosis. Data from recent

trials will be compared with those reported by the Netherlands Interuniversity Cardiological Institute of 533 consecutive patients clinically thought to have myocardial infarction. In 269 patients assigned to streptokinase (SK) either with intracoronary administration within four hours or to the same regimen with 500 000 U SK given intravenously upon admission as well, death rate at a mean of eight months follow up was 23 (8.5%) *vs* 41 (15.5%) in 264 conventionally treated patients. This reduction in mortality, longer than that for any previously reported treatment, if confirmed by further trials requires a rethinking of the assignment, distribution, and availability of health resources. The fact that rTPA (a human plasminogen activator) given intravenously in the same time span yields similar patency rates ($\pm 75\%$ *vs* 85% in the ICI study) emphasises the involvement of first line medical resources. Arguments will be provided why this additional expenditure may be cost saving in the long run.

Is localised intracoronary hyperkalaemia a risk of laser angioplasty?

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A potential danger of laser angioplasty may be toxic byproducts of photo-vaporisation of atheroma, arterial wall, or blood. To assess whether the laser energy which will penetrate atheromatous plaque can also haemolyse sufficient red blood cells to cause dangerous localised intracoronary hyperkalaemia we irradiated 20 samples of fresh heparinised human blood with different types and wavelengths of laser, that is pulsed and continuous wave Nd-YAGB (1060 nm); argon (488 and 514 nm); and pulsed excimer laser at 351 nm (XeF), 249 nm (KrF), and 193 nm (ArF). With pulsed and continuous Nd-YAG lasers the total energies delivered per ml of blood were those which in vitro will give either 1 mm (100 J and 60 J respectively) or 3 mm (300 J and 180 J respectively) plaque penetration. With the argon laser we used pulse energies per ml of blood which in vitro will penetrate plaque by 0.1, 0.2, 1, 2, and 5 mm. The respective total energies delivered with the excimer laser penetrate up to 0.16 mm. Potassium concentrations ($[K^+]$) were measured by flame photometry. With the argon laser $[K^+]$ was continuously monitored during laser application by a potassium sensitive electrode capable of detecting $[K^+]$ changes down to 0.44 mmol/l. Post-laser $[K^+]$ s with argon (4.5–5.1 mmol/l) and all three excimer

(3.8–4.1 mmol/l) wavelengths lay within the control range (3.7–5.4 mmol/l, six samples), and the potassium sensitive electrode detected no change during argon laser application. With both types of Nd-YAG laser, however, there was a pronounced increase in $[K^+]$ to 7.5–7.7 and 17.4–20.5 mmol/l, for the 1 and 3 mm plaque penetration energies respectively.

In conclusion intracoronary argon laser energy (of twice that which will cause immediate coronary perforation) did not give a $[K^+]$ change of more than 0.5 mmol/l (that is lysis of 84 million red blood cells); nor did lower doses of pulsed XeF, KrF, or ArF laser energy; both types of Nd-YAG laser are likely to give localised intracoronary hyperkalaemia especially if plaque penetration of 1 mm or more is attempted with each energy delivery; and this is probably due to deeper penetration of longer wavelengths into blood and hence more extensive red blood cell damage.

Attenuation by calcium blockade of the abnormal response to cold pressor stimulation in patients with ischaemia and normal coronary arteries

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This study was designed to investigate the effect of nisoldipine, a calcium antagonist, on the left ventricular and peripheral haemodynamic response to cold pressor stimulation in 12 patients with angina and normal coronary arteries. All patients had chest pain, evidence of ischaemia on exercise electrocardiograms, and abnormal responses to exercise on radionuclide angiography. Patients were imaged at rest and after 1 minute and 2.5 minutes of cold pressor stimulation before and after 10 mg of oral nisoldipine. Radionuclide angiograms were performed using gold-195 m (half life of 30.5 s). Before nisoldipine mean (SD) left ventricular ejection fraction fell from 61 (9)% at rest to 55 (9)% at 1 minute of cold pressor stimulation, and 56 (8)% at 2.5 minutes cold pressor stimulation (both $p < 0.01$ *vs* rest). Ten patients showed an abnormal ejection fraction response to cold pressor (fall in ejection fraction of $\geq 5\%$). Nisoldipine caused a rise in mean (SD) resting heart rate from 83 (12) to 92 (21) beats per minute and a fall in resting systolic pressure from 145 (30) mm Hg to 136 (25) mm Hg. Both heart rate and systolic pressure rose significantly, however, from rest to both stages of cold pressor before and after nisoldipine. Moreover the cold induced increases in heart rate and systolic pressure from resting levels were not attenuated by nisoldipine at

either stage. After nisoldipine, left ventricular ejection fraction was 63 (10)% at rest, 64 (9)% at 1 minute cold pressor, and 65 (6)% at 2.5 minutes cold pressor (not significantly different) and only three patients had an abnormal response. Left ventricular ejection fraction was significantly higher at each cold pressor stage compared to pre-nisoldipine values ($p < 0.001$).

In conclusion (a) abnormal response to cold pressor is common in patients with ischaemic syndromes and normal coronary arteries, (b) this response is largely blocked by a calcium antagonist, and (c) this effect is not mediated by blocking the heart rate and systolic pressure responses to cold stimulation and is possibly related to inhibition of cold induced coronary vasoconstriction.

Double blind comparison of the effect of increasing diuretics or adding captopril in the treatment of moderate cardiac failure

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Ten patients with heart failure who remained symptomatic despite treatment with 40 mg of frusemide daily were included in a randomised double blind crossover study to compare the effect of increased doses of diuretics with the addition of captopril. The patients were considered to have moderate heart failure clinically and as measured by their exercise tolerance. All patients were maintained on 40 mg of frusemide throughout the study. They were treated in random order with an extra 40 mg of frusemide daily for two weeks followed by an extra 80 mg of frusemide for a further two weeks, and with the addition of captopril 25 mg three times a day for two weeks followed by 50 mg three times a day for two weeks. Between treatments there was a single blind period in which placebo tablets were added to the standard frusemide 40 mg. Mean (SEM) symptom-limited exercise tolerance measured on a treadmill increased from 13 (1.2) minutes to 15.6 (0.9) minutes at the end of the period of extra frusemide ($p < 0.01$) and from 13.4 (1.2) minutes to 14.9 (0.9) minutes at the end of captopril treatment ($p < 0.05$). Venous occlusion plethysmography showed that both treatments caused arteriolar and venous vasodilatation in the limbs. In these patients with moderate heart failure increased diuretics produced a more favourable short term response than captopril.

Assessment of ventricular function in aortic regurgitation by phase analysis of equilibrium radionuclide ventriculography

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An objective non-invasive measure of early changes in left ventricular (LV) function in chronic aortic regurgitation (AR) would be helpful in deciding the timing of valve replacement. In this study phase analysis of equilibrium radionuclide ventriculography was compared with LV ejection fraction (EF), regurgitant index, and clinical assessment. In 15 control subjects LV phase spread (standard deviation of LV phase values) was $8.0 (2.6)^{\circ}$ (mean (2 SD)). A group of 27 patients with chronic AR were divided independently into those with clinically mild (group I, $n=8$), moderate (group II, $n=10$), and severe (group III, $n=9$) disease. Mean LV phase spread was normal at rest in groups I ($8.2 (2)^{\circ}$) and II ($8.9 (2.4)^{\circ}$) and increased in group III ($12.9 (3.7)^{\circ}$) (mean (SD): II vs III, $p < 0.05$). Phase spread was abnormal in 1/8 in group I, 2/10 in group II, and 8/9 in group III. EF was normal in all patients at rest and fell by > 0.05 in six patients (three in group II, three in group III). In six patients with symptoms phase spread was abnormal in 6/6 but EF fell on exercise in only 2/6. The regurgitant index correlated poorly with measures of LV function.

Changes in regional wall motion defined by phase analysis are more sensitive than global EF in detecting abnormalities in LV function due to AR.

Ten year clinical evaluation of models 6400 and 6120 Starr-Edwards isolated mitral valve replacement

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Performance characteristics differ significantly between various currently available heart valve prostheses. To determine the long term outcome of Starr-Edwards (S-E) mitral valve replacement we identified 286 patients discharged from hospital who had isolated mitral valve replacement with S-E models 6400 or 6120 during 1974-1983. We followed up 279 (97.5%) patients to 1984—a total of 1573 patients-years. Mean age at implantation was 51.6

years, 39.4% were male, and eight (2.87%) had had previous mitral valve replacements. Ten year mortality was 40 deaths (2.54% patient-years) of which 26 (1.65% patient-years) were cardiac in origin and eight of these (0.50% patient-years) were directly valve related. Reoperation was necessary in 13 (4.65%); three (1.07%) because of thromboembolism, four (1.43%) for infective endocarditis, and six (2.15%) for paraprosthetic regurgitation, all within the first two years. Total 10 year valve-related morbidity was 32 (2.03% patient-years) due to thromboembolism 16 (1.01% patient-years), anticoagulant related haemorrhage four (0.25% patient-years), prosthetic endocarditis four (0.25% patient-years), haemolysis two (0.12% patient-years), and paraprosthetic regurgitation six (0.38% patient-years).

This current prosthesis based assessment documented satisfactory long term performance characteristics of the S-E mitral models 6400 and 6120 without any recorded episodes of mechanical valve dysfunction and compares favourably with other available mitral prostheses.

The assessment of surgical shunt patency by Doppler

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Range gated pulsed Doppler echocardiography was used to evaluate the patency of surgically created systemic-pulmonary artery anastomosis in 41 children with cyanotic congenital heart disease and right ventricular outflow tract obstruction. There were 26 Blalock-Taussig and 15 Waterston shunts. In 24 cases the shunt was diagnosed as being patent by placing the Doppler sample volume within the lumen of the shunt as identified on cross sectional imaging and obtaining the characteristic systolic and diastolic flow pattern. A further 11 patients in whom the shunt was not located on cross sectional image had systolic and diastolic turbulent flow in the pulmonary artery and its branches (systolic turbulence alone was present preoperatively). Thirty two of the 33 patients with Doppler diagnosed patency had clinical evidence of shunt patency (good colour, continuous murmur). In one case with Doppler patency the patient was mildly cyanosed but colour improved once ventilation perfusion imbalance was corrected. Three shunts were shown to be completely blocked by finding no flow within shunt lumen (1) or no evidence of any diastolic flow in the pulmonary artery or its branches (2). These were confirmed to be non-patent at cardiac catheterisation (2) and necropsy (1). Of the remaining six clinically non-patent

shunts low amplitude Doppler turbulent signals were present either within the shunt or in the region of shunt insertion to the pulmonary artery. These were considered to be partly blocked and this was confirmed at cardiac catheterisation (5) and operation (1).

This study confirms that pulsed Doppler echocardiography is a useful tool for assessing shunt patency after operation.

Anatomic correction for transposition and DORV—early and intermediate structural and functional considerations

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Thirty five patients have undergone anatomic correction of transposition of the great arteries (TGA). Ten had intact ventricular septum (TGA/IVS), 17 had ventricular septal defect (TGA/VSD), and eight had double outlet right ventricle with subpulmonary VSD (DORV). Their ages ranged from 18 hours to 6 years (mean 11.3 months) and their weights from 2.6–16.4 kg (mean 6.1 kg). The TGA/IVS group on average was younger (mean 1.2 months) and smaller (mean 3.6 kg) than the other two groups. Eleven patients had pulmonary artery banding, four repair of coarctation, four had atrial septectomy, and two had systemic/pulmonary artery shunts performed. Thirty day hospital mortality was two in TGA/IVS, six in TGA/VSD, and one in DORV. There have been no late deaths. Fifteen patients have undergone cardiac catheterisation and angiography from one to four years following operation. There has been satisfactory growth of the great vessels at the site of the anastomoses. In one patient there is narrowing of the right coronary artery. Aortic regurgitation has not been demonstrated. The mean left ventricular-aortic pressure gradient was 6 mm Hg and the right ventricular-pulmonary artery gradient was 29 mm Hg. More precise examination of left ventricular function by frame by frame analysis of ventriculograms indicated normal volumes, ejection fraction, and shape index changes in all. In six patients regional wall motion was normally synchronous and symmetrical. In six there was minor hypokinesis of the free wall, associated with delay in the onset of inward motion. Significant asynchrony occurred in three, affecting the inferior wall in two and the free wall in one. These changes may reflect the effects of cardiopulmonary bypass, the correction of volume overload, or transient interference with coronary flow.

Pulmonary atresia in prenatal life

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Of seven cases of pulmonary atresia with intact ventricular septum recognised by echocardiography in prenatal life, five have had gross dilatation of the right heart. This is unusual compared with postnatal series in which a dilated right ventricle is uncommon unless there is associated Ebstein's anomaly. The criteria for diagnosis of pulmonary atresia were failure to visualise the valve opening on systole, no forward flow through the main pulmonary artery in the three cases evaluated by Doppler, or failure to demonstrate a connection between the main pulmonary artery and the right ventricle. Cases where these findings were present but the tricuspid valve attachment was displaced were not included in this study. In the cases with right ventricular dilatation, the right ventricular:left ventricular ratio ranged from 1.4 to 3.5 compared with a normal ratio of 1.0 (0.2). The main pulmonary artery was smaller than the aorta in each case, ranging from 0.5 to 0.75, compared with a normal ratio of 1.4 (0.4). Tricuspid incompetence was demonstrated in the two cases evaluated by Doppler. The degree of lung compression in the five cases with enlarged right ventricles appeared to contribute significantly to the universal mortality in these cases in our series—one intrauterine death, two stillbirths, two neonatal deaths. Relief of the cardiac enlargement during pregnancy to allow normal lung development during the last weeks of pregnancy seems to be the logical method of approach. Will catheter-mediated intrauterine surgery ever be able to achieve this?

Does elective hypothermic circulatory arrest cause brain damage? Influence of its duration and other perioperative variables in patients with congenital heart disease

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Surgical repair can be enhanced by use of hypothermic circulatory arrest (15°C) when treating very small patients with complex congenital heart disease. Brain type isoenzyme creatine kinase (CK-BB) is known to be released after brain injury. Blood concentrations of CK-BB were measured before and after circulatory arrest and were related to the

duration of circulatory arrest and other perioperative variables with a known or assumed impact on the magnitude of brain injury in 20 patients weighing less than 8 kg with complex congenital heart disease who were operated on while in profound hypothermic and circulatory arrest achieved by topical cooling and core cooling to 15°C. Samples were obtained from arterial and internal jugular venous blood for analysis of CK-BB before and for 20 hours after operation (23 specimens from each patient), and were analysed by a two site monoclonal antibody technique. CK-BB concentrations increased from 3.5 (0.5) (mean (SEM)) mg/ml to a peak average of 27 (9) mg/ml (range 3.5–240). Venous concentrations increased significantly more than arterial concentrations, indicating a release into the cerebral venous effluent. The CK-BB concentration curves were positively related to the arrest time ($r=0.9$), post-arrest blood glucose concentration ($r=0.69$), preoperative haemoglobin concentration ($r=0.42$); and were negatively related to age ($r=-0.67$), post-arrest pH ($r=-0.78$), and post-arrest haemoglobin concentration ($r=0.76$). The correlation coefficient for preoperative oxygen saturation versus CK-BB was -0.41 ($p < -0.02$) for the group and -0.61 ($p < 0.05$) for those with cyanosis.

These results suggest that plasma analysis of CK-BB can quantify brain dysfunction and that oxygen desaturation at levels found clinically may be detrimental, giving further support for early rather than late corrective surgery in patient with cyanotic congenital heart disease.

The fate of adults with tricuspid atresia and normally related great arteries

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Nineteen patients aged 15–39 years (mean 24) with tricuspid atresia and normally related great arteries were reviewed to determine their quality of life and exercise capacity using a symptom limited treadmill exercise test (ET) (modified Bruce protocol). Fourteen had ≥ 1 shunts before 14 years and eight had a shunt before one year. Ten patients had a Fontan operation at 9–22 years (group A, mean age now 22) and nine had either a shunt (8) or no surgery (1) (group B, mean age now 27). The 10 in group A are New York Heart Association grade I or II; one is slightly cyanosed from a small atrial septal defect. Nine lead a normal life and eight are working or attend normal school. Nine performed the ET; four reached stage II; three stage III, and two stage IV. Seven of group B are New York Heart Association

grade I or II and two are grade III; all are cyanosed. Six lead a normal life, but only four are working. All performed the ET and two only reached stage I; three stage II; three stage III; and one stage IV. Left ventricular ejection fraction measured by radio-nuclide angiography was similar in group A (mean 47%) and eight of group B (mean 46%) and did not correlate with exercise capacity.

Survival with tricuspid atresia into the fourth decade is possible exceptionally, even without prior surgery. Fontan survivors have slightly better exercise tolerance than those with shunts, who are less likely to work. Despite possible deleterious effects on left ventricular function from longstanding shunts, however, patients can have a good quality of life after simple shunting procedures.

The clinical significance of ventricular supernormal period in man

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Clinical assessment of the supernormal period (SNP) (the interval where a subthreshold stimulus can excite the ventricle) was performed in 23 patients during routine electrophysiological studies (7 for syncope, 2 for conduction defects, 9 for supra-ventricular arrhythmias, and 5 with ventricular tachycardia (of whom two were on amiodarone)). The SNP was assessed with a cathodal and anodal single ventricular extrastimulus after 8 beats of constant rate atrial pacing at 100 bpm. The cathodal diastolic threshold was significantly lower than anodal (0.48 (0.2) vs 1.2 (0.5) mA, $p < 0.01$). A SNP (defined as being equal to or $> 5\%$ less than diastolic threshold) was demonstrated in all but three patients. A cathodal SNP was seen in 20 patients but only 12 (61%) had an anodal SNP. Cathodal SNPs were more sharply defined but significantly smaller than the anodal SNPs (51 (42) vs 103 (54) ms, $p < 0.05$). In patients with no ventricular tachycardia 72% of the cathodal SNPs were within the QT interval measured during atrial pacing at bpm (QT, 370 (28) ms), but only 51% of the anodal SNPs were within the QT interval. In three patients who had inducible ventricular tachycardia only 5% of the cathodal SNPs were within the QT interval (QT, 330 (25) ms). In two patients with ventricular tachycardia largely controlled with amiodarone, 92% and 54% of the cathodal SNP was within the QT interval. Thus SNP can be determined clinically and may be a useful electrophysiological assessment of the potential for ventricular tachycardia.

Automatic diagnosis of ventricular tachycardia by new methods of electrogram analysis

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Pulse generators are implanted specifically for the management of ventricular tachyarrhythmias (VT). The diagnosis of VT by such a device is based on heart rate analysis and is therefore susceptible to confusion with other tachycardias such as sinus tachycardia. A diagnostic method which is independent of heart rate criteria is essential. Since the shape of endocardial electrograms is altered by changes of rhythm, we have compared three methods of electrogram analysis for their ability to distinguish VT from sinus rhythm: fast Fourier transformation (FFT), gradient pattern detection (GPD), and intrinsic deflection timing (IT). Simultaneous bipolar and unipolar electrograms from the right ventricular apex were recorded between 0.016 and 1 kHz during sinus rhythm and 11 different VT from 10 patients. Bipolar electrograms were then analysed by FFT and by GPD, a program which memorises the sequence of gradients within an electrogram (based on a computerised first differential of the electrogram) and detects arrhythmias when the pattern of gradients changes. The third method, IT, was applied to unipolar electrograms and consists of measurement of the time (t) between the initial and intrinsic deflections of these electrograms. With altered ventricular depolarisation sequence t also changes allowing VT to be recognised.

Frequency analysis by FFT discriminated VT from sinus rhythm on only seven occasions whereas GPD and IT, which rely on analysis of electrogram morphology, were successful in 10 of the 11 examples. The changes in t within unipolar electrograms produced by VT ranged from 15 to 65 ms (mean 38.75 ms). Both GPD and IT failed to distinguish the same VT which was right ventricular septal in origin. Analysis of electrogram morphology by GPD and IT will prove useful in the automatic diagnosis of VT by implantable devices.

Haemodynamic and symptomatic improvement using dual chamber pacing in hypertrophic cardiomyopathy

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Patients with hypertrophic cardiomyopathy in

whom drugs have failed to control symptoms and in whom surgery may not be feasible present a difficult management problem. Four patients were studied, three complained of dyspnoea, New York Heart Association grade III, one grade IV, and all had maximum drug therapy before assessment. Cardiac catheterisation had been carried out previously and echocardiography was repeated before study. Haemodynamics were assessed before and during temporary dual chamber pacing using flow directed thermodilution catheters. Results showed a fall in pulmonary capillary wedge pressure from 12 (3) mm Hg pre-pacing to 9 (2) mm Hg post-pacing with no change in systemic pressure. Cardiac output was maintained, being 4.45 (1.47) l/min pre-pacing and 4.57 (1.57) l/min post-pacing. The atrioventricular (AV) delay showing the best haemodynamic response at rest was 150 msec, close to the resting P-R interval; short AV delays did not maintain cardiac output or reduce pulmonary capillary wedge pressure to the same extent. On the basis of these results permanent (DDD) pacemakers were implanted with an AV delay of 150 msec. Patients noted an impressive clinical response, with two becoming asymptomatic and two becoming grade I without previous drug therapy. Echocardiographic follow up (mean 12 months) showed a reduction in mitral leaflet systolic anterior motion and less outflow tract obstruction. We conclude that dual chamber pacing improves haemodynamics in hypertrophic cardiomyopathy, and this is reflected in a pronounced symptomatic improvement and left ventricular outflow obstruction is lessened.

Adaptation of overdrive pacing rate for termination of AV re-entry tachycardia with change in posture—relevance for automatic software pacemakers

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The recent introduction of software-based pacemakers for terminating re-entry atrioventricular (AV) tachycardia has permitted the use of algorithms that can adapt to the acceleration of tachycardia under differing physiological conditions. Atrial systems are available which terminate tachycardia by producing second degree block within the AV node. We have assessed the relation between the rate of tachycardia and the rate at which second degree block develops in the AV node in seven patients with AV re-entry tachycardia undergoing electrophysiological study. All had presented with sustained episodes of tachycardia and had been resistant

to treatment with 4-7 oral antiarrhythmic agents. The patients, aged 18-45 years, were being investigated for their suitability for antitachycardia pacing. During sustained tachycardia, rapid atrial pacing, consisting of a train of 10 beats, was delivered at a rate 10 beats a minute faster than the tachycardia. The rate of the bursts of rapid atrial pacing was increased by a further 10 beats a minute until AV nodal block was produced and the arrhythmia was terminated. The test was undertaken with the patient lying and then repeated while the patient was standing. In each case the rate of tachycardia increased from the lying (135-210, mean 174 bpm) to the standing (145-240 bpm, mean 205 bpm) position and this was accompanied by an increase in each case of the rate required to cause AV nodal block. The cycle length of atrial pacing required was 93-80% of the tachycardia cycle length when the patients were lying down and 88-68% when the patients were standing. There was not a uniform degree of percentage shortening with change in posture; four patients required a greater difference on standing with three demonstrating no change in the ratio. In three patients implantation of permanent anti-tachycardia pacemakers confirmed this relation. Incorporation of these data into algorithms for termination of re-entry AV tachycardia will not only allow more rapid adaptation of burst pacing for termination under differing physiological conditions but will also permit use of the minimum effective termination rate and so minimise the risk of producing atrial fibrillation.

Analysis of the signal averaged surface electrocardiogram for late potentials after myocardial infarction

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Late potentials are low voltage oscillations detectable within the terminal QRS of the signal averaged surface electrocardiogram. Late potentials alone or a wide QRS (110 ms) may be predictors for re-entry ventricular tachycardia. We have studied the importance of these electrocardiographic features in patients after myocardial infarction. Major processing problems include a poor signal to noise ratio for late potentials and accurate QRS timing. We have combined signal averaging with additional processing methods including (a) subtraction of a polynomial fit from the original averaged electrocardiogram and (b) high pass frequency domain

filtering. These methods are simple and complementary and have advantages over the bi-directional time-domain filtering and vector magnitude calculation that are usually employed. Of 40 patients after myocardial infarction 15 had a positive result, five with late potentials, four with a wide QRS, and six with both. Twenty healthy controls were negative. Five of the 15 positives had a left ventricular aneurysm compared with one of 25 negatives. Positive results were found more often when a submaximal exercise test (5 mets) was abnormal (12 of 28 patients) than when it was normal (3 of 12). No difference was found between positive and negative groups in the incidence of ventricular tachycardia induced by programmed stimulation, and clinical follow up (8 months) showed no difference in clinical ventricular tachycardia, which occurred in one patient from each group.

Ambulatory pulmonary artery pressure monitoring in the evaluation of angina pectoris

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A method for the continuous measurement of ambulatory pulmonary artery (PA) pressure using a transducer tipped catheter and a simple recording system has been developed. PA pressure is recorded on a miniaturised tape recorder and played via an optical writer and analysed beat-to-beat. The transducer tipped catheter has been validated against a conventional fluid-filled system, and changes in left ventricular end diastolic pressure are faithfully reflected in changes in PA diastolic pressure. We have investigated haemodynamic changes during ST depression. Continuous 24 hour ambulatory PA monitoring was performed in 17 patients with coronary artery disease. We have compared the changes during 36 daytime anginal episodes with those during a treadmill exercise test (modified Bruce). On exercise the onset of PA preceded ST segment depression in 15/17 patients whereas during spontaneous episodes this occurred in 9/34 cases. The magnitude of PA increase and ST depression were not significantly different. On cessation of exercise the PA diastolic pressure returned to basal more rapidly (0.5 min, range 0.2–102) than did the ST segment (6.2 min, range 0.1–25.9 [$p < 0.01$]). During two painful episodes and two exercise tests there was a significant rise in PA diastolic pressure but no change in the ST segment. In five patients with normal coronary arteries presenting with chest pain, there was no significant change in the PA diastolic

pressure on exercise. Thus, ambulatory pulmonary artery pressure monitoring is a useful technique in the evaluation of patients with angina.

Coronary vasodilatation by calcitonin gene related peptide

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The primary RNA transcript of the calcitonin gene can be modified in a tissue specific manner to give alternative mRNA's, one of which encodes the calcitonin gene related peptide (CGRP). This circulating peptide, a potent systemic vasodilator, is widely distributed in the nervous and cardiovascular systems and has been identified in the periaortic nerves of the coronary arteries. We studied the effect on coronary artery diameter of infusion of saline as control followed by CGRP in incremental doses into the left coronary artery. Six patients were examined during routine angiography. Four patients had atypical chest pain and normal coronary arteries and two had variant angina with coronary spasm superimposed on non-critical lesions. The maximum dose of 200 ng/min for 5 minutes was 1/20th of the maximum systemic dose reported and caused no systemic effect other than mild facial flushing. Coronary arteriography was repeated after each infusion period and epicardial vessel diameter was measured manually and by use of a CASS computer system. No effect of saline was found but a dose dependent increase in arterial diameter occurred during CGRP infusion. The maximum increase in proximal circumflex, and in proximal, mid, and distal left anterior descending artery diameter was 35%, 20%, 21%, and 83% respectively, with a 32% increase at the site of the two atheromatous lesions. Intracoronary injection of 15 µg CGRP relieved ergometrine induced pain, ST elevation, and coronary spasm in two patients, though prior infusion had not prevented the spasm.

The demonstration of dilatation of coronary arteries as well as vascular location and systemic vasodilation suggest that CGRP could have a role in the control of vascular smooth muscle tone.

The effects of beta blocker, calcium antagonist, and nitrate in patients with exertional and rest angina

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There is controversy about the mechanisms and treatment of rest angina. Some believe that vasomotor tone alteration is important, whereas others have shown increases in myocardial oxygen demand before onset of ischaemia. We investigated the effects of atenolol 100 mg a day, nifedipine 20 mg three times a day, and isosorbide mononitrate 40 mg twice a day given for five days each in a double blind trial in nine patients (eight with three vessel disease and one with single vessel disease) with coronary artery disease and frequent daytime and nocturnal pain and ambulatory ST changes. During the last 48 hours of each treatment period patients kept angina diaries and had treadmill exercise testing and ambulatory ST monitoring performed. There was significant reduction in the number and duration of episodes of ST change with atenolol when compared with nifedipine and isosorbide (atenolol *vs* nifedipine, 23% ($p < 0.01$) (atenolol *vs* isosorbide, 34% ($p < 0.01$)). Nocturnal episodes were reduced with all three drugs. Pain frequency was greater with isosorbide than with atenolol ($p < 0.01$). Only one patient had improvement in exercise tolerance with nifedipine compared with atenolol, whereas the others exercised more or to an equal workload with atenolol. This patient had single vessel disease and coronary tone alteration which may have been an important factor. Overall, beta receptor blockade was the most effective means of reducing myocardial ischaemia occurring at rest and exercise and should be considered as first line therapy.

Spontaneous variability of ventricular arrhythmia and its effect on the optimal duration of electrocardiographic monitoring required

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The biological variability of arrhythmia determines the duration of electrocardiographic monitoring and the percentage reduction of arrhythmia necessary to demonstrate therapeutic efficacy. We have assessed the variability of ventricular extrasystoles and the duration of electrocardiographic monitoring necessary to exclude ventricular tachycardia, using 16 patients with hypertrophic cardiomyopathy and ventricular tachycardia as a model population. They had 48–168 hours of monitoring (median 72) off treatment in a one year period; 108 episodes of ventricular tachycardia (0–10, mean 1.5 per day) were recorded (52% incidence). Daily ventricular extrasystole rates were 2–17 693 (median 172). Analysis of variance showed a difference in ventricular extra-

systole counts between corresponding eight hour and 24 hour periods of 48% and 38% respectively. A sine curve fitted to these counts showed a circadian rhythm with a peak frequency in the afternoon (50%) and night (50%). A 73% reduction in mean ventricular extrasystole frequency on corresponding eight hour or a 61% reduction on consecutive 24 hours periods was necessary to attribute with 95% confidence an effect to intervention rather than to spontaneous variability. The likelihood of excluding ventricular tachycardia on K days of electrocardiographic monitoring with various rates of occurrence was determined. The probability of failing to detect ventricular tachycardia was 48% for 24 hours of monitoring, 23% for 48 hours, and 11% for 72 hours. We conclude that for patients with hypertrophic cardiomyopathy and ventricular tachycardia 48–72 hours of electrocardiographic monitoring is appropriate to assess drug intervention for ventricular tachycardia; and that the demonstration of a circadian rhythm for ventricular extrasystoles indicates that similar hours of monitoring should be compared in the assessment of an intervention effect.

Evidence that flecainide is superior to disopyramide in suppressing chronic ventricular premature complexes

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A double blind cross over comparison of flecainide 200 mg twice daily and disopyramide 150 mg four times daily was used to assess efficacy and safety in 13 patients (six with ischaemic heart disease and seven with hypertensive, valvar, or cardiomyopathic disease). Each patient had more than 100 ventricular premature complexes (VPCs) during a 24 hour Holter monitor screen. Each active treatment period lasted 14 days, followed by seven days on placebo. At the start of the trial and at the end of each week 24 hour Holter monitoring was performed. Blood samples for drug assay were taken at the end of each treatment or placebo period. Median suppression of placebo VPC frequency was 94% for flecainide and 53% for disopyramide ($p < 0.03$). Greater than 80% suppression occurred in 69% of patients during flecainide and in 38% during disopyramide treatment ($p < 0.01$). Complex arrhythmic events, including ventricular tachycardia, were significantly less common during flecainide treatment. Two patients during flecainide and two during disopyramide had at least a twofold increase in VPC frequency compared with control, indicating proarrhythmic effects. The incidence and severity of side effects including gastrointestinal and neurological symptoms were

comparable for both treatments. Blood pressure and heart rate were not altered by either agent. Flecainide produced greater prolongation of PQ and QRS intervals than disopyramide, sometimes exceeding normal values. The mean trough blood concentrations for flecainide (686 (135) ng/ml) and disopyramide (3.26 (0.29) μ g/ml) were within therapeutic ranges.

These findings confirm that flecainide is more effective than disopyramide in suppressing chronic VPCs and complex ventricular arrhythmias, with no increase in the incidence of side effects.

Reverse delta wave: a reliable sign of impending ventricular fibrillation in right coronary angiography

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In a prospective study 22 episodes of ventricular fibrillation (VF), occurred during coronary angiography over three years. In 20 cases ECG lead I was recorded initially and just before the onset of VF. In four cases VF followed left coronary injection of contrast medium and in 16 it followed injection of the right coronary artery or right aortocoronary graft. In all but one of these cases the development of a characteristic ECG sign was observed before the onset of VF. This consists of an S wave having a sharp downstroke and a slurred upstroke with a width of at least 100 ms. The pattern resembles the delta wave of Wolff-Parkinson-White syndrome but inverted and reversed. In eight cases the reverse delta wave was the only abnormality preceding VF, in one case there were also frequent coupled ventricular extrasystoles, in three cases there were sinus pauses, and in three cases the onset of VF was obscured by artefact. An analysis of 50 unselected coronary angiograms from patients with a similar age and sex distribution and severity of coronary disease showed the occurrence of the reverse delta wave in only two cases, in both of which S waves of at least 40 ms width were present in the initial ECG. A lesser version of the pattern with duration of 40–80 ms was recorded transiently after right coronary artery injections in 31 cases.

The reverse delta wave of at least 100 ms duration, suggesting delayed depolarisation of part of the ventricular myocardium to the right side, possibly the pulmonary conus, was thus a consistent and specific indicator of impending VF occurring, as the great majority did, during right coronary angiography.

Contrasting effects of the class III agents amiodarone and sotalol in ischaemic myocardium

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The cellular electrophysiological effects of amiodarone and sotalol were compared in the isolated perfused interventricular septum of the rabbit heart during control perfusion and ischaemia. Five rabbits were treated with oral amiodarone for 2–3 months and in seven sotalol (10^{-4} mol/l) was added to the perfusate. There were eight control septa in the amiodarone group and seven in the sotalol study. Before ischaemia amiodarone caused a non-significant increase of 12% in action potential duration (APD₉₀) and 7% in effective refractory period (ERP). Action potential upstroke velocity ($\dot{V}_{max}$) was reduced by 25%. In contrast, sotalol caused increases of 52% in APD₉₀ and 31% in ERP, with no effect on $\dot{V}_{max}$. During 30 minutes' zero-flow ischaemia, APD₉₀ shortened in the amiodarone, sotalol, and control groups, such that neither drug maintained a persistent class III effect. The ERP in the sotalol group became significantly shorter than in controls, while in the amiodarone group there was gross lengthening of ERP with loss of 1:1 capture in 3/5 muscles. The fall in $\dot{V}_{max}$ during ischaemia was accentuated by amiodarone but lessened by sotalol.

The class III effects of both amiodarone and sotalol disappear in the ischaemic myocardium. Amiodarone exerts a major class I action during ischaemia, while sotalol preserves the sodium channel, possibly because of a slowing of the rate of accumulation of extracellular potassium. These effects may account for some of the differences in the therapeutic profiles of these two "class III" drugs.

Arrhythmias and left ventricular hypertrophy in essential hypertension

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Electrocardiographic (ECG) evidence of left ventricular hypertrophy is a strong risk factor in hypertension and is not closely related to the level of blood pressure. In primary hypertrophy (hypertrophic cardiomyopathy) ventricular arrhythmias are common, and sudden death is known to occur. We investigated the frequency of ventricular arrhythmias by 48 hour ambulatory monitoring in 90 treated

hypertensive patients and 30 normotensive control subjects; in addition, all patients had a standard 12 lead ECG and cross sectional echocardiography from which left ventricular mass was calculated using the short axis area-length method. Ventricular tachycardia (VT) (≥ 3 complexes) occurred in 13 (14%) of 90 hypertensive patients and in none of the controls ($p < 0.01$). There were no differences in age or in duration of hypertension in patients with or without VT, although blood pressure levels (mmHg) were slightly higher in those with VT ($169.5(6.7)/110.1(8.3)$ vs $152.5(2.6)/98.3(2.1)$, $p < 0.05$). In those with VT ECG evidence of left ventricular hypertrophy was more common and left ventricular mass was significantly greater ($221.9(21.6)$ g vs $157.1(6.6)$, $p < 0.01$). Forty hypertensive patients (44%) had no ECG evidence of hypertrophy: VT was less common in this group (3 of 40), but couplets and ventricular extrasystoles occurred more commonly than in the control group and mean left ventricular mass was significantly higher ($148.5(9.8)$ g vs $111.9(6.7)$ g, $p < 0.01$).

Thus ventricular arrhythmias are common in patients with left ventricular hypertrophy secondary to hypertension and occur with increasing frequency and complexity as left ventricular mass increases; as with other forms of cardiac hypertrophy, the increased mortality associated with left ventricular hypertrophy in hypertensives may be related to the frequency of ventricular arrhythmias.

Potassium homeostasis following acute myocardial infarction—the effect of beta blockade

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To document the effects of acute myocardial infarction (AMI) on potassium homeostasis, erythrocyte (RBC) and plasma (P) potassium were measured serially in 36 patients with definite AMI. Six of these subsequently developed primary ventricular arrhythmias (VA), another five were on chronic diuretic treatment (DT), and 22 cases were uncomplicated (UC). Eleven of the 36 patients received intravenous metoprolol followed by oral metoprolol and 10 received an identical regimen of placebo. Sampling was performed on admission, a mean of 8 hours after symptom onset; one hour later; at 24 hours; and 5–7 days later. Plasma potassium (mmol/l (1 SD)) was significantly lower on admission in both VA ($3.62(0.2)$) and DT ($3.60(0.36)$), compared with

UC patients ($4.17(0.4)$) ($p = 0.0008$, $p = 0.03$). By 24 hours only the DT patients remained hypokalaemic ($3.57(0.44)$) (VA $3.90(0.26)$, UC $3.99(0.34)$) ($p = 0.02$). Thus, normokalaemia was achieved within the first 24 hours in the VA patients ($p = 0.007$) but was delayed in the DT patients ($p = 0.02$). RBC potassium (mmol/kg dry weight of erythrocytes) was higher on admission in the VA patients ($287(32)$) (DT $244(33)$, UC $262(35)$, $p = 0.07$). This difference became significant at 24 hours (VA $294(29)$; DT $256(25)$; UC $258(25)$, $p = 0.01$). There were no differences in either RBC potassium or plasma potassium between the metoprolol and placebo treated patients. To investigate further the use of beta blockade in the prevention of post-infarction hypokalaemia, plasma potassium was measured on admission in 30 consecutive patients with definite infarction who were only excluded from the previous study because they were taking chronic beta blockade. Admission plasma potassium was significantly higher in the beta blocked patients ($4.38(0.42)$) compared with the 36 patients not taking beta blockade ($4.00(0.42)$) ($p = 0.002$). The 12 patients taking concurrent diuretic therapy were equally protected ($4.12(0.42)$, $3.60(0.36)$ ($p = 0.03$)). Both selective (14) and non-selective (16) agents appeared equally effective.

We conclude that changes in cellular as well as plasma potassium occur early after AMI, particularly in patients developing VA, and could be adrenergically mediated. Chronic but not acute beta blockade is effective in the prevention of post-infarction hypokalaemia.

Exercise induced ST elevation post-infarction: prognostic importance and relation to site of infarct

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The prognostic importance, the mechanism, and the relation of exercise induced ST segment elevation to the site of infarction are unclear. Of 339 consecutive patients with acute infarction, 222 had a submaximal pre-discharge stress test. The sites of infarction were anterior in 94 (42%) patients, inferior in 76 (34%), posterior in 6 (3%), and subendocardial in 46 (21%). ST shift was recorded in 109 patients: ST depression in 62 (28%), ST elevation in 77 (35%), and both elevation and depression in 30 (13%) patients. New or additional ST elevation occurred in 73 (42%) of

the 176 patients with Q wave infarcts and in four (9%) of the 46 patients with non-Q wave infarcts ($p < 0.0001$). In patients with Q wave infarcts, ST elevation always developed over the site of recent infarction, occurring in 54 patients with anterior infarcts and in 19 with inferior infarcts. Exertional ST elevation was significantly more frequent in patients with anterior than in those with inferior infarcts ($p < 0.001$) but was not, among those with anterior infarcts, significantly associated with ST segment depression in the inferior leads. By univariate analysis, induced ST elevation was predictive of death during a mean follow up of 14 months (range 6–36 months).

Therefore, predischARGE post-infarction exertional ST elevation is of prognostic importance and appears to be influenced chiefly by the site and type of infarct.

Effect of amiodarone on arrhythmia and left ventricular function in heart failure

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Although ventricular arrhythmias are common in heart failure and are associated with a poor prognosis conventional antiarrhythmic treatment is often complicated by further myocardial depression. We compared amiodarone (200 mg/day, after a one week loading of 600 mg/day) in 22 patients aged 56 (8) years, of whom 19 were men and all of whom had heart failure due to left ventricular dysfunction of New York Heart Association class II or III, with identical placebo in a double blind crossover study with three month treatment periods. Patients were selected on the basis of heart failure rather than arrhythmia. The median daily dose of frusemide was 120 mg/day and 10 were also receiving captopril. Visual analogue scores for breathlessness were similar on placebo and amiodarone (29 (17) vs 26 (14) cm respectively). Resting heart rate fell from 79 (12) on placebo to 70 (10) beats per minute ($p < 0.01$) but blood pressure was unaffected. Treadmill exercise performance (modified Bruce protocol) also was unimpaired and resting and exercise ejection fraction were similar on placebo and amiodarone (12.2 (3.8) vs 12.7 (3) minutes, 24 (10) vs 25 (12)%, and 25 (14) vs 28 (13)% respectively). Amiodarone reduced ventricular extrasystoles (900 vs 175 per 24 h, $p < 0.001$, median values), complex ventricular arrhythmias (27 vs 2 per 24 h, $p < 0.001$), and ventricular tachycardia

(9 vs 0 per 24 h, $p < 0.001$). Three patients died on placebo and two were withdrawn from amiodarone, one with a developing myocardial infarction and another with worsening atypical ventricular tachycardia.

Amiodarone suppresses ventricular arrhythmias without deterioration in cardiac status as assessed by symptoms, exercise performance, and radionuclide ventriculography in patients with heart failure. Occasionally it may exhibit proarrhythmic effects.

Lipoprotein profiles in veteran endurance athletes and age matched subjects with coronary artery disease and controls

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Increased plasma total cholesterol, very low density lipoprotein (VLDL), and possibly total triglyceride concentrations may be associated with an increased risk of coronary artery disease (CAD). In contrast, high density lipoprotein (HDL) and in particular its subfraction HDL₂ has been shown to have a strong negative correlation for the presence of CAD. Strenuous exertion has been shown to have a beneficial effect on plasma lipoproteins. The long term effects of exercise training on plasma lipoproteins, however, have not been described. We measured plasma lipoproteins in 20 male lifelong endurance runners with a mean age of 52 years, a group of normal controls, and a group of subjects with known CAD. All groups were closely matched in terms of age, body mass index, and dietary fat intake. Plasma total cholesterol was slightly higher in those with CAD ($p = \text{NS}$). Plasma total-triglyceride, however, was significantly increased compared with both controls and athletes, as was VLDL which was raised in both controls and those with CAD ($p < 0.01$). Total HDL was higher in the athletic group than in the controls ($p < 0.01$) and in subjects with CAD ($p < 0.05$). Plasma HDL₂ was significantly higher in the runners 67 (25.1) mg/dl than in the controls (49 (26.7) mg/dl, $p < 0.001$) and in those with CAD (33 (22.5) mg/dl, $p < 0.001$). HDL₃ was significantly lower in controls. Thus the HDL₂ to HDL₃ ratio was 0.286 in athletes, 0.243 in controls, and 0.155 in those with CAD ($p < 0.01$).

These results suggest that habitual endurance improves the plasma lipoprotein profile with regard to risk for CAD.

Is myocardial metabolism uniform?

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Fatty acids are important substances for myocardial metabolism at rest and during ischaemia. The myocardial handling of radioisotope labelled fatty acids is thought to provide a measure of myocardial metabolism as well as perfusion. Iodine-123 labelled heptadecanoic acid can be imaged using a standard mobile gamma camera interfaced to a computer for the analysis of washout curves for the whole heart and the three regions of interest appropriate to the three major coronary arteries. Sixteen apparently healthy volunteers (10 males and 6 female) were scanned in the 30°–40° left anterior oblique projection after the administration of 40 mBq of fatty acid. Initial distribution of fatty acid mirrored that of thallium-201. Mean left ventricular fatty acid washout ($t_{1/2}$ in minutes) was similar for males (40.1 (2.1) min) and females (41.5 (5.7) min). In the left ventricular territory supplied by the left anterior descending artery, mean washout was 35.4 (1.5) min in men and 38 (4.8) min in women. Washout was slower in the territory supplied by the circumflex artery (44 (2.8) min male, $p < 0.01$; and 42.5 (4.9) min female) and considerably slower in the inferior portion of the ventricle supplied by the right coronary artery (51.3 (2.8) min male, $p < 0.01$; and 54 (7.1) min female, $p < 0.05$). No background subtraction was used because regions of interest over the lung generated washout curves suggestive of active metabolism, and blood clearance curves suggested an acceptably low measure of activity within 15 min in males and a mean of 11 min in females.

In conclusion, there appear to be significant regional differences in myocardial metabolism, and this has implications in the assessment of the patient with coronary artery disease.

Non-invasive haemodynamic assessment of mitral prosthetic function by Doppler ultrasound

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Forty one patients with a mitral valve prosthesis (28 tissue, 13 mechanical) were assessed by means of

pulsed and continuous wave Doppler ultrasound. Cardiac catheterisation including biplane left ventricular angiography was performed in 38 patients. Mean valve gradients were obtained in 28 patients and ranged from 0 to 18 mm Hg (mean 5.8 mm Hg). Continuous wave Doppler was performed from the apical position using a Vingmed Alfred Velocimeter in conjunction with spectrum analysis and valve gradients were calculated using the modified Bernoulli equation. Mean Doppler gradients ranged from 0 to 12 mm Hg (mean 5.4 mm Hg) and correlated well with those obtained independently at catheterisation ($r = 0.85$). One patient with significant prosthetic stenosis at catheterisation was correctly identified by a prolonged mitral pressure half-time of 410 ms (compared with < 200 ms in all non-obstructed prostheses) and two patients with obstructed mechanical prostheses (mitral pressure half-time > 500 ms) had operation without catheterisation. Mitral regurgitation was identified in 17 patients at angiography (mild in four, moderate in three, and severe in 10). Continuous and pulsed wave Doppler performed in all patients detected mitral regurgitation in 16 of the 17 patients and the extent of left atrial turbulence correlated well with the severity of regurgitation at angiography ($r = 0.88$).

In conclusion, pulsed and continuous wave Doppler ultrasound can provide an accurate non-invasive haemodynamic assessment of mitral prosthetic valve function.

Sensitivity of echocardiography in infective endocarditis

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We prospectively studied 55 consecutive patients with a first episode of native valve endocarditis to evaluate the sensitivity of cross sectional echocardiography in the depiction of valvar vegetations and the potential sources of error. The underlying cardiac abnormality was of non-rheumatic origin in 26 patients with the infection located at the aortic valve in 12, the mitral valve in 10, and the tricuspid valve in four. In 20 others the heart was previously normal with the aortic valve involved in eight, the mitral valve in six, aortic and mitral valves in one, and tricuspid valve in five. Only nine patients had previously had valve abnormalities of rheumatic origin (six aortic, two mitral, one aortic and mitral).

Vegetations were recognised in 34 (62%) patients, two of whom also had aortic root abscess. Seven more were found to have vegetations at operation or at necropsy (false negatives). No false positives were identified among 29 patients with anatomic confirmation of vegetations. The sensitivity of cross sectional echocardiography in predicting vegetations was 78% in patients who previously had a valvar abnormality of non-rheumatic origin, and all of the vegetations that were missed involved heavily calcified aortic valves. Sensitivity was 93% in those who previously had a normal heart but only 33% in patients with rheumatic heart disease. The overall sensitivity of the method was 76%. There was no difference in the predictive accuracy according to which valve was infected.

Cross sectional echocardiography is a sensitive method for detecting vegetations and intracardiac abscesses except in rheumatic valve disease and calcific aortic stenosis, when its diagnostic accuracy is low.

Inappropriate left ventricular hypertrophy in mild hypertension: echocardiographic study in middle aged subjects

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A prospective echocardiographic study was performed in 106 patients (35–60 years) with hypertension. Patients were excluded if there were other causes of left ventricular hypertrophy (LVH), myocardial infarction, or LV dilatation. LVH (posterior wall or septal thickness ≥ 1.3 cm) was present in 67 (64%) and was severe (≥ 1.8 cm) in 31 (29%). Most hypertensives showed a linear relation with a significant ($p < 0.001$) but modest correlation between the systolic blood pressure (BP) and LV mass and ratio of wall thickness to cavity radius (H:R) ($r = 0.77$ and 0.51 respectively). Seven patients, however, could be identified with mild hypertension (systolic BP 145–165 mm Hg) who differed in their LV response to increased systolic BP. Their LV mass and H:R were at least as great as those found in severe hypertensives and their calculated systolic wall stress was substantially lower. These seven patients appear to have inappropriate LVH. In this group of patients with inappropriate LVH there was a relatively uniform echocardiographic appearance with pronounced wall thickening and a small to normal sized LV cavity. The peak rate of dimension increase and wall thin-

ning were significantly reduced from normal ($p < 0.001$). The presence of severe LVH in mildly hypertensive patients was a relatively common finding and such patients appear to present a consistent echocardiographic appearance with a small hypertrophied ventricle and abnormal diastolic properties. These findings are important because LVH is a strong predictor of increased cardiovascular mortality.

Pitfalls in the comparison of Doppler estimates of aortic flow velocities with cardiac catheterisation data

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We have compared the Doppler derived peak left ventricular-aortic pressure gradient with the peak to peak gradient measured at catheterisation in 30 consecutive cases. Three cases of aortic stenosis with unsatisfactory recordings were excluded. In the remaining 27 cases an excellent correlation (0.82) was obtained between the two methods. While underestimation of jet velocities is a technical pitfall, there are also conceptual pitfalls, especially when the Doppler gradient exceeds the catheter gradient; our series included five such examples. In these, the differences in gradient between the two methods were 82, 47, 36, 36, and 29 mm Hg. The major explanation for these differences is that the peak Doppler gradient is an instantaneous gradient which is not equivalent to the peak to peak pressure gradient measured at catheterisation which measures two non-instantaneous pressures. The maximum instantaneous gradient is greater than the peak to peak one, with the difference diminishing as the severity of an aortic stenosis increases. Thus, in mild aortic stenosis the Doppler gradient exceeds the peak to peak gradient, a difference enhanced by increased flow with aortic regurgitation. Echo-catheter observations separated in time and variations in heart rate also contribute to differences. All five of our anomalous cases had moderate or severe aortic regurgitation with increased aortic flow as the prime cause of unexpectedly high Doppler velocities. To avoid such pitfalls, attention should be directed towards the spectral signal in aortic valve disease; the morphology of forward jet velocities; the morphology, intensity, and mapping of aortic regurgitant velocities; and the subvalvar velocities. Peak Doppler gradients are often compared with peak to peak gra-

dients with generally good results, but unless the incompatibility of the two measurements is recognised, misleading clinical data will be obtained in certain cardiac conditions.

Assessment of pulmonary hypertension by two Doppler echocardiographic methods

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Non-invasive assessment of the degree of pulmonary hypertension is of prime clinical importance. Using two Doppler echocardiographic methods we have estimated pulmonary artery (PA) systolic pressure in 21 patients undergoing cardiac catheterisation. The cardiac abnormality was rheumatic in eight, coronary disease in four, mitral valve prolapse in three, congestive cardiomyopathy in three, and calcific aortic valve disease in two. In one patient no organic heart disease was documented. The main PA flow velocities and the flow velocities of tricuspid regurgitation (TR) were recorded at each Doppler study. From the spectral display of pulmonary velocities obtained, the time to peak velocity (TPV) and the right ventricular ejection time (RVET) were measured. The maximum velocity of TR (V_{max}) was determined from the spectral trace and the modified Bernoulli equation ($\text{gradient} = 4 \times V_{max}^2$) was applied to find the peak gradient between the right ventricle and the right atrium. A small correction was made for right atrial pressure estimated clinically and the right ventricular systolic pressure thereby derived. In the absence of obstruction this is equivalent to systolic PA pressure. In five patients no TR could be documented but in four of them systolic PA pressure was 31 mm Hg or less. In two patients no PA velocities could be detected. Tricuspid regurgitation estimated systolic PA pressure, TPV, and TPV/RVET were correlated with the systolic PA pressure measured at cardiac catheterisation (r values 0.96, -0.49, -0.38 respectively). Time to the peak of the pulmonary artery velocities correlated poorly with systolic pulmonary artery pressure, but this interval may be altered by several factors, especially the compliance of the vascular bed. Pulmonary artery pressure derived from the trans-tricuspid gradient showed an excellent correlation with that obtained at cardiac catheterisation. Provided there is tricuspid regurgitation this method provides extremely useful clinical information.

Coronary blood transit: effects of nifedipine assessed by parametric digital subtraction angiography

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Blood flow through stenotic coronary arteries and the effects of nifedipine have been investigated in six patients with left anterior descending coronary artery disease ($>70\%$ stenosis). The heart rate is fixed by pacing. Selective left coronary contrast injections were imaged with an ECG gated digital system, providing three 256×256 pixel matrices per cardiac cycle. In the present algorithm, contrast density is plotted against time for each pixel. Colour coded cardiac images are provided in which areas sharing common times to attainment of peak contrast density are indicated by isochrones (the T_{max} image). A further program generates an isochrone map based on times to attainment of half peak contrast density (the $T_{1/2max}$ image). Times have been expressed in terms of cardiac cycles. At basal heart rate T_{max} was attained within 8–13 cardiac cycles of first contrast injection in all myocardial areas; all patients showed antero-septal T_{max} and $T_{1/2max}$ delays of 1–2 cycles on isochrone images. After sublingual nifedipine (10–20 mg) shortening of T_{max} and $T_{1/2max}$ by two cardiac cycles occurred in the post-stenotic territory in two patients, with a one cycle reduction in the remaining four subjects. Sub-anginal overdrive pacing (three subjects) further shortened T_{max} and $T_{1/2max}$ in both normal and under-perfused regions, but did not further reduce regional perfusion uniformity as assessed by this method.

This technique is sensitive to physiological changes in coronary flow rates. Results suggest that rates of flow to the heart downstream of a coronary stenosis can be improved with nifedipine.

Magnetic resonance assessment of left ventricular wall motion

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Magnetic resonance provides high resolution images

of the heart allowing non-invasive assessment of cardiac structure and function. This study investigates the validity of left ventricular wall motion determined by magnetic resonance. Coronal and sagittal magnetic resonance images were acquired at end diastole and end systole through the aortic valve and the plane of widest diameter of the left ventricle respectively, using a Picker International machine (0.24 tesla). These images were compared with anteroposterior and lateral x ray contrast ventriculograms by two independent observers. The left ventricular wall was divided into three segments, and the motion of each segment was classified as normal, hypokinetic, akinetic, or dyskinetic. Muscle thickness was classified as either normal or thin in the systolic magnetic resonance images. 18 patients were studied—2 normal subjects, 9 with previous myocardial infarction, 4 with coronary artery disease without infarction, 1 with congestive cardiomyopathy, 1 with mitral stenosis, and one with an atrial septal defect. One lateral ventriculogram was uninterpretable; thus there was a total of 105 segments. Wall motion comparisons were the same in 68 segments, differed by one class in 32 segments, and by 2 classes in 5 segments. In three of these 5, magnetic resonance showed the segment to be akinetic and thin at the site of a previous infarct, whereas ventriculography showed normal motion. The fourth was in the patient with atrial septal defect, in whom magnetic resonance showed paradoxical septal motion which was confirmed by echocardiography. In the fifth, magnetic resonance showed normal motion without thinning, and ventriculography showed akinesis in a patient with coronary artery disease without infarction. These differences may be explained by the difference between the tomographic section and an x ray projection. Magnetic resonance showed 20 segments to be thin, and these were all in subjects with previous myocardial infarction. Only 1 subject with infarction (3 months previously) did not have an area of wall thinning.

Magnetic resonance provides an accurate non-invasive assessment of left ventricular wall motion and wall thinning.

Myopotential sensing and DDD pacemakers

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Myopotential sensing is a well recognised problem with VVI pacing. Therefore, we have looked particularly for this potential hazard in our patients with DDD pacemakers where there is the possibility of both atrial and ventricular sensing, in order to find out whether myopotential sensing or inhibition is a significant problem in these patients. Seventy-four patients with DDD pacemakers were routinely assessed by a standard test of pectoral muscle stimulation. In addition 38 patients had 24 hour ECG (Holter) monitoring done 3–5 days and one month after implantation. The result from standard testing showed that ventricular inhibition was commonly produced (63% of patients) but this appeared to be responsible for symptoms in only a small number (15%) of patients. Atrial sensing was less common (16%) but produced symptoms in a much greater proportion of patients (42%). The results from the 24 hour ECG tape recordings showed similar findings: 55% of patients were found to have episodes of ventricular inhibition (up to 4.6 s), which occasionally occurred during sleep; 11% had atrial sensing; and the percentage of patients with symptoms was also similar (14% ventricular, 50% atrial). The symptoms were abolished by reprogramming the pacemaker in all but one patient (although some units have inadequate sensitivity ranges).

This study shows that myopotential sensing is common with DDD pacemakers and that routine testing by pectoral muscle stimulation is as good a screening test as 24 hour ECG monitoring.

A modified energy delivery system for lower energy ablation

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Ablation of atrioventricular (AV) nodal conduction has been performed with low energies and active fixation electrodes. These catheter electrodes have high internal resistances and therefore alter the delivered energy time relation. We have investigated whether a modified energy system would allow successful ablation using standard USCI electrodes and lower energies. In vitro experiments were performed with various resistors. A USCI plus 50 ohms produced a waveform with characteristics similar to the Helifix without a guidewire. Ten patients were treated, five male and five female. Nine had paroxysmal atrial fibrillation (AF) and one had dual AV nodal pathways. The energy delivery system consisted of a standard defibrillator with a 50 ohm resistor

in series with the electrode output. The stored and delivered energy was measured. All shocks were delivered cathodally via the distal electrode of a 6F bipolar USCI pacing lead. Using a stored energy of 200 J (delivered energy 99 J), these patients all developed complete heart block immediately after the procedure. Lower delivered energies failed to produce complete heart block. Four patients required one shock and six patients required two shocks (maximum total energy delivered 198 J). Six patients remain in complete heart block while two have first degree AV block and right bundle branch block (RBBB). These eight patients remain asymptomatic and have permanent pacemakers. Two patients remain symptomatic, both have RBBB, one with additional first degree block.

Therefore 80% of our group are asymptomatic on no drug treatment. There were no complications. Energy requirements for successful ablation of AV nodal conduction can be reduced somewhat for the USCI electrode if a modified energy delivery system is used. This remains less efficient, however, than the method incorporating an active fixation electrode.

Idiopathic infantile hypercalcaemia (Williams-Beuren syndrome) and associated cardiac anomalies: a clinical and echocardiographic study

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Idiopathic infantile hypercalcaemia (IHC) is often recognised to be associated with supra-valvar stenosis and peripheral pulmonary artery stenosis. Occasionally, however, there have been reports of other associated cardiac abnormalities. As there was no previous large cardiological survey analysing the incidence and types of various cardiac defects seen with this syndrome, the present study was designed. Sixty six IHC patients with a mean age of 10 years were studied. A complete cardiovascular examination including recordings of blood pressures in both arms and legs was carried out. Cross sectional echocardiographic (CSE) recordings were made in all standard echocardiographic planes. Pulsed Doppler echocardiography (PDE) was used to detect any abnormal flow across the cardiac chambers and valves. In 58 (88%) cases the blood pressures were normal for age, being raised in only six (12%) cases. In 17 (25%) cases there were clinical features sug-

gestive of peripheral pulmonary artery stenosis but CSE and PDE demonstrated the lesion in only two of these 17 cases because of the more peripheral site of obstruction. Coarctation of aorta was resected in two (3%) cases and two others had reconstruction of aortic root. Echocardiography showed that (a) in 60 (95%) of 62 unoperated cases in which a good echocardiogram could be obtained there was evidence of abnormal indentation at the sinotubular junction and Doppler showed varying turbulence depending on the severity of obstruction with minimal or no turbulence in those cases with absent neck murmurs; (b) eight (12%) cases had bicuspid aortic valve; (c) eight (12%) cases showed associated mitral valve prolapse; and in three (5%) cases there was valvar pulmonary stenosis, with one of these cases having associated ventricular septal defect.

This study indicates that although abnormal aortic root and peripheral pulmonary stenosis are the important cardiac anomalies associated with IHC, the occurrence of other associated defects is not uncommon.

Doppler echocardiography following anatomical correction of transposition of the great arteries

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Nineteen patients who had undergone anatomical correction of transposition of the great arteries between the ages of 1 week and 10 years were studied by pulsed and continuous wave Doppler echocardiography one month to 98 months following operation. Systolic aortic velocities were normal in all but one patient, but mild aortic regurgitation was detected in 10. Elevated flow velocities either at pulmonary level, at the pulmonary artery bifurcation, or in the left pulmonary artery were detected in fourteen patients. Adequate Doppler sampling of the right pulmonary artery was not achieved. The site of obstruction to pulmonary flow and the presence and severity of aortic regurgitation detected by Doppler echocardiography correlated well with cardiac catheterisation performed in 16 patients at a mean interval of 35 months before study by Doppler. Peak velocities across the atrioventricular valves were found to be significantly higher than normal, suggesting that ventricular compliance in this group of patients may differ from normal. No pathological atrioventricular valve regurgitation was seen. The

principal limitation of Doppler echocardiography in this study was the inability to obtain flow velocities from the right pulmonary artery. Doppler echocardiography provides valuable information following the arterial switch operation and may avoid the need for repeat cardiac catheterisation.

Hypoplastic left heart syndrome and 45X karyotype

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In reviewing 63 patients with 45X karyotype (Turner syndrome) admitted to our institution over the period 1972–85, 20 (31.7%) had one or more cardiac malformations (mostly coarctation and aortic stenosis). Of these 20, four (20%) died in the neonatal period with an hypoplastic left heart syndrome (HLHS). One infant had a severe mitral and aortic stenosis with a very small left ventricle and died at age of 35 days. The other three had a typical HLHS including aortic atresia and died between the second and seventeenth day of life. In three of the four cases Turner syndrome (TS) was clinically suspected. One of the clinically suspected TS had a mosaicism (46XX, 45X); the other three had a 45X karyotype.

Forty patients were admitted to our department during the same period with the diagnosis of HLHS; there were 15 girls and 25 boys. Of the 15 girls, four (26.6%) had 45X karyotype. The high incidence of HLHS in TS and of TS in girls with HLHS has not been recognised in published reports, and HLHS should be added to the list of expressions of the 45X karyotype. This study also accords with the flow theory in which coarctation is regarded as a consequence of a slight degree of fetal left ventricular obstructive disease, HLHS being as extreme form of the same malformation.

Echocardiography and ambulatory electrocardiography in patients with tuberous sclerosis

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The purpose of this study was to estimate the incidence of echocardiographic and electro-

cardiographic abnormalities in patients with tuberous sclerosis. Eleven patients with tuberous sclerosis agreed to participate in the study. Their ages ranged from 4 years to 38 years (mean (SD) 20.3 years (13)). All patients underwent cross sectional echocardiography and 24 hour ambulatory ECG monitoring. In seven of the eleven cases echo dense nodules ranging from 3 mm to 12 mm in diameter were detected within the myocardium. These masses occurred most commonly in the ventricular septum, but they were also seen in the posterior left ventricular wall and papillary muscles. In patients with abnormal echocardiograms, sinus tachycardia at rates up to 150 beats per minute occurred in two patients during seizures and in two it was unrelated to seizures; paroxysmal abrupt sinus slowing occurred in three; and supraventricular tachycardia at rates up to 150 beats per minute in two. One patient with a normal echocardiogram showed ventricular pre-excitation with paroxysmal tachycardias at rates up to 180 beats per minute.

In conclusion, echocardiographic abnormalities suggestive of rhabdomyoma are commonly seen in patients with tuberous sclerosis. Echocardiography should be routinely performed in such patients. Ambulatory ECG monitoring may detect disturbances in cardiac rhythm in some cases and should be considered when there are symptoms suggestive of a possible cardiac rather than a cerebral aetiology.

Functional correlates of cardiac rejection from intramyocardial markers

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The motion of seven radio-opaque midwall markers implanted at operation was followed in eight patients at fixed intervals (10–14 days) over 70–165 days after orthotopic cardiac transplantation. On the same day as right ventricular myocardial biopsy, each patient had cineradiography of his markers at 100 frames/s in either biplane 30° right anterior oblique (RAO) and 60° left anterior oblique (5 patients) or single plane 30° RAO (3 patients). A radio-opaque sphere of known diameter was imaged at the level of the heart to determine the correction factor for x ray magnification. Marker volumes were calculated by the area-length method using a computer assisted system, and ejection fraction, peak ejection rate, and peak filling rate were derived. Ejection fraction, end

systolic volume, and peak ejection rate remained almost constant over the period of observation. At times of severe rejection, as evidenced by myocyte necrosis in the biopsy specimen, however, there was a reduction in end diastolic volume and in peak filling rate. Thus systolic function was preserved but diastolic function was deranged, a pattern similar to that seen in early restrictive cardiomyopathy. After resolution of rejection, end diastolic volume and peak filling rate returned to baseline values. Compared with histological evidence of severe rejection, the functional correlates from markers yielded a sensitivity of 86% and a specificity of 94%.

In conclusion (a) histological evidence of severe rejection in transplanted hearts is associated temporally with abnormal diastolic function and relative preservation of systolic function of the left ventricle, and (b) serial cineradiography of implanted markers in transplanted hearts may be a useful non-invasive tool for timing myocardial biopsy to detect rejection.

Do hyperkalaemic cardioplegic solutions damage vascular endothelium?—studies on vascular responsiveness in the rat heart

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Although cold chemical cardioplegic solutions are widely used for myocardial protection during open heart surgery, their effects on the vascular endothelium have not been characterised in detail. Protection of the vascular endothelium should be of great importance since damage to it predisposes to platelet deposition, atherosclerosis, thrombus formation, and myocardial infarction. Using the isolated Langendorff perfused rat heart, we measured the effect on coronary flow (ml/min) of optimally active concentrations of either 5-hydroxytryptamine (1×10^{-7} mol/l) or papaverine (5×10^{-6} mol/l). The drugs were added to the perfusate (37°C, 60 cm H₂O perfusion pressure) for a three minute period before and after 30 minutes of hypothermic infusion (20°C, 100 cm H₂O) with a cardioplegic solution containing 25 mmol/l potassium. Before cardioplegia both 5-hydroxytryptamine and papaverine caused a similar increase in coronary flow (+21.2(1.6)% and +22.8(1.6)% respectively; eight hearts in each group). After cardioplegia the response to 5-hydroxytryptamine was completely lost and a slight vasoconstriction was observed (−0.2(1.2)%), whereas there was no significant change in the response to papaverine which maintained a

+23.7(1.4)% vasodilatation. Since 5-hydroxytryptamine is thought to exert its vasodilatory effect mainly via the release of an endothelium dependent relaxant factor, the results indicate that hyperkalaemic crystalloid cardioplegic solutions may injure the endothelium or some aspect of its function. This conclusion is reinforced by the maintenance of the vascular response to papaverine which acts directly on the smooth muscle cells and is independent of the endothelium.

Do cardiac glycosides exert positive inotropism in sinus rhythm?

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In this bicentenary year of cardiac glycosides the debate centres around whether digitalis can exert positive inotropism in heart failure with sinus rhythm. Using a newly developed analytical method which enables us to identify inotropic changes in an exercising patient, this question was studied in 10 cardiac failure patients (New York Heart Association classes III and IV) at rest and during exercise. Haemodynamic data were collected before treatment (C), after acute intravenous ouabain (O), and after six weeks of maintenance treatment with digoxin (D). There were no detectable inotropic changes at rest after either glycoside. During exercise, however, three of the patients after ouabain and six after chronic digoxin therapy demonstrated true positive inotropic effects, as shown by greater hydraulic power outputs of the hearts, compared with those achieved during C, that could not be accounted for by alterations in peripheral resistance, heart rate, or filling pressure. The heart rates during exercise were not significantly different (125 (8.6) C, 120 (7.3) O, and 122 (4.5) D bpm). There were significant falls in left ventricular filling pressures from 39 (3) mm Hg (C) to 34 (3) (O) ($p < 0.06$), and to 33 (3) (D) ($p < 0.02$). The cardiac hydraulic power outputs for all patients rose significantly from 1.54 (0.63) W (C) to 1.80 (0.67) W (O), ($p < 0.01$) and 1.96 (0.85) W (D), ($p < 0.01$).

In conclusion, both intravenous ouabain and chronic oral digoxin can exert true positive inotropic effects during exercise but not at rest in a subset of heart failure patients with sinus rhythm.

Sensitivity and specificity of coronary artery bypass graft patency estimation by cine computed tomography

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The sensitivity of cine computed tomography (CCT) in the determination of coronary artery bypass graft patency was assessed. Computed tomographic scans were performed on the Imatron C-100 scanner in two views (transaxial and 20° oblique) at eight simultaneous contiguous 1 cm levels from the ascending aorta at the level of the highest myocardial graft clip through the aortic root to the level of the proximal coronary arteries. The scan time was 50 ms with an 8 ms interscan delay. Scans were performed with ECG triggering every other beat at the peak of the R wave over a period of 20 cardiac cycles. A bolus of 35–39 ml of contrast was injected intravenously, over a period of 3–6 s depending on catheter diameter. All injections were made with a Medrad injector. Results in 21 patients, four female and 17 male, aged 32–77, with 51 grafts were compared with those of cardiac catheterisation. Forty-seven (92%) of 50 grafts were correctly identified by CCT. One further graft was identified by CCT which was not present by catheterisation. Overall accuracy was 90%. Thirty-four of 37 patent grafts were correctly identified (92% sensitivity) and 13 of 14 occluded grafts (93% specificity). Time density contrast curves were constructed from areas of interest placed in the ascending aorta and in the grafts and the curves were compared to assess graft flow. Graft flow was designated as good if the time density curve in the graft corresponded to the aortic curve and poor if there was delayed contrast clearance. Flow in the grafts could also be assessed visually by projecting the flow study in a movie mode format. This aided in graft identification (two false positive results). Streak artefact was considerably reduced compared with conventional CT. Of the 46 patent grafts, qualitative flow evaluation in 45 by CCT agreed with catheterisation.

Beneficial effect of beta blockade in aortic stenosis

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Pharmacological treatment of patients with significant aortic stenosis and preserved left ventricular systolic function is controversial. This study was performed to evaluate the effects of beta blockers in such patients. Fifteen consecutive symptomatic patients with aortic stenosis (gradient > 50 mm Hg, ejection fraction > 55%) underwent technetium-99m radionuclide cineangiography and exercise electrocardiography in the basal state and after one week of 100 mg atenolol daily. During atenolol there was a decrease in resting heart rate (72(14) to 58(12) beats per minute, $p < 0.01$), and in systolic (124(25) to 107(12) mm Hg, $p < 0.05$) and diastolic arterial pressure (83(12) to 70(7) mm Hg, $p < 0.01$). Exercise induced angina and dyspnoea were improved in all patients; exercise duration increased from 7.0(2.5) min to 11.4(2.7) min, ($p < 0.001$). Peak ejection rate, time to peak ejection rate, ejection time, peak filling rate, time to peak filling rate, and time of exercise were compared. During atenolol treatment peak ejection rate decreased from 3.1 (6) to 2.6 (6) edv.s^{-1} ($p < 0.05$), ejection time increased from 386 (27) ms to 421 (32) ms ($p < 0.01$), and peak filling rate increased from 2.43 (0.7) to 2.72 (0.7) edv.s^{-1} ($p < 0.05$). There was no change in the ejection fraction, time to peak ejection rate, and time to peak filling rate.

These results indicate that beta blockers can be used safely and beneficially in symptomatic patients with aortic stenosis and preserved left ventricular systolic function. Their efficacy is probably due to lengthening of diastole with improvement of ventricular filling and coronary blood flow. Though sudden death might thereby be prevented the benefits should not encourage delay in aortic valve replacement.

Effects of enalapril on renal function in heart failure

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Since glomerular filtration rate (GFR) in heart failure is thought to be maintained by constriction of the efferent arteriole by angiotensin II, treatment with angiotensin converting enzyme (ACE) inhibitors could impair renal function. We investigated the effects of enalapril and placebo in a double blind study on blood pressure, renal function, and plasma angiotensin II after one week (acutely), after eight weeks (chronically), and one week following with-

drawal of treatment. Acutely, enalapril lowered mean blood pressure from 105 (15) to 95 (20) mm Hg ($p < 0.01$) but increased effective renal plasma flow (ERPF) from 305 to 320 ml/min; however, GFR and filtration fraction fell from 71 (23) to 62 (19) ml/min ($p < 0.01$) and from 0.26 to 0.20 ($p < 0.01$). Chronically, ERPF increased further to 348 ml/min ($p < 0.01$), though mean blood pressure fell further to 88 mm Hg ($p < 0.005$), as did GFR and filtration fraction to 57 (22) ml/min and 0.17 (0.05) respectively ($p < 0.01$). Plasma angiotensin II concentrations which were similar at both times during treatment (12(9) and 9(5) pmol/l) returned to pre-treatment concentrations (64(32) pmol/l one week after withdrawal. Despite this, ERPF remained increased at 320 ml/min and mean blood pressure reduced at 95 mm Hg ($p < 0.05$) but GFR returned to placebo values at 67 ml/min. During chronic enalapril treatment there was no evidence of total body sodium retention despite the fall in blood pressure and GFR; clinical improvement occurred and exercise time increased ($p < 0.01$). Thus the effects of ACE inhibitors on renal function are complex, time related, and cannot be attributed entirely to suppression of circulating angiotensin II.

Cardiovascular fitness improves the coronary risk profile

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The continuing popularity of jogging may be fuelled at least partly by the belief that it has a preventive effect on the development of coronary heart disease. We investigated the effects on coronary risk factors, body composition, and cardiac function of a 30 week structured running programme in 26 sedentary middle aged men (mean age 43 (2) years) entering their first marathon. Mean total jogging time increased from 1 to 8 hours per week; body weight fell from 78.2 (10.2) to 74.7 (9.4) kg (mean(SD)) and body fat, calculated by densitometry, from 24 (3) to 20 (3)% (all $p < 0.001$). Mean caloric expenditure which was estimated from oxygen consumption measurements obtained during treadmill exercise and from diary mileages was 64 000 kcal; despite the fall in body weight and fat there was an increase in mean caloric consumption of 1000 kcal per week. Fasting plasma cholesterol concentration fell from 6.4 to 5.7 mmol/l ($p < 0.01$) but high density lipoprotein cholesterol did not change (1.18 and 1.23 (0.4); triglycerides

fell from 1.52 (0.8) to 1.26 (0.5) mmol/l ($p < 0.02$). Resting systolic blood pressure fell from 132 (15) to 113 (16) mm Hg ($p < 0.001$) and diastolic blood pressure from 84 (16) to 74 (10) mm Hg ($p < 0.05$). Eleven men smoked initially (range of consumption 10–60 cigarettes per day) but eight had stopped by the end of the study. Cardiovascular fitness as assessed by maximum oxygen uptake increased from 34 l (6) to 38.7 (5) ml/kg/min ($p < 0.001$). Thus dynamic exercise training reduced the blood pressure, body weight, body fat, and plasma lipids and increased cardiovascular fitness, leading to a pronounced improvement in coronary risk profile.

Impairment of left ventricular function in diabetics—evidence for a specific heart muscle disease

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Diabetes is a major risk factor for death from heart disease, but the relative contributions of large and small vessel disease to the impairment of left ventricular function previously noted in diabetic patients is unclear. We investigated left ventricular function in 56 asymptomatic long standing insulin dependent diabetics aged 30–49 years who had had diabetes for 6–35 years (mean 17 years) and in 30 age and sex matched non-diabetic controls by means of radio-nuclide ventriculography at rest and during supine dynamic exercise. Mean resting left ventricular ejection fraction (LVEF) (56%) in diabetics was normal and was no different from that in controls (54%). During exercise, ejection fraction rose less in diabetics (9.0%) than in controls (13.7%, $p < 0.005$). The exercise response was abnormal—that is failed to rise by $> 5\%$ in 18 diabetics, of whom three developed repolarisation abnormalities on exercise electrocardiography. Coronary arteriography was performed in eight patients with an abnormal exercise ejection fraction response and showed no evidence of large vessel coronary artery disease in any subject. Myocardial biopsy specimens showed features consistent with a diabetic microangiopathy in all diabetic patients with thickening of precapillary arterioles and interstitial fibrosis on light microscopy, and basement membrane thickening or reduplication on electron microscopy.

Thus the left ventricular functional impairment which was present in one third of these asymptomatic diabetic patients during exercise may be due to a specific diabetic heart muscle disease.

Correspondence

Radionuclide ventriculography in coronary artery disease

Sir,

The title of the paper by Dr Wieshammer and colleagues—"Limitations of radionuclide ventriculography in the non-invasive diagnosis of coronary artery disease" (1985; 53:603-10)—deserves comment, lest it be taken to imply that radionuclide ventriculography is of limited use in the management of patients with coronary artery disease. For the title to have reflected all the findings of the study it would have been more reasonable to have omitted the words "radionuclide ventriculography in".

Sensitivity and specificity depend upon the population sampled, and the figures in this paper are not generally accepted experience because of the very low frequency (25%) of coronary artery disease in the patients studied. Most British cardiologists would not expect three quarters of coronary arteriograms performed for the investigation of chest pain to be normal, and the point is well made that classic angina is the best indicator of the presence of disease. My own experience at the Middlesex Hospital, gained from a population defined in the same way as that of Wieshammer *et al* (albeit with a higher frequency of coronary artery disease), is that the figures for sensitivity and specificity of left ventricular ejection fraction are 94% and 90% respectively, and as assessed by the standard deviation of the phase histogram the figures are 88% and 85% respectively.¹

The precise figures are not however the point at issue, since no test without perfect specificity is suitable for screening in a population with a low incidence of a disease. More importantly, left ventricular function during stress gives an indication of the functional importance of coronary artery disease, and is therefore of prognostic value in patients with established disease. Irrespective of their coronary artery anatomy, patients without evidence of ischaemia at maximum exercise do well without intervention.²

It would be unfortunate if the report of Wies-

hammer *et al* deterred cardiologists unfamiliar with radionuclide ventriculography from making use of the important contribution this technique can make to patient management.

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This letter was shown to the authors, who reply as follows:

Sir,

In reply to Dr Underwood's comments we wish to re-emphasise that our study assessed the role of radionuclide ventriculography in the primary diagnosis of coronary disease only. We have neither stated nor implied that it is of limited value in the management of patients with established coronary disease but rather we share Dr Underwood's opinion about its usefulness in the latter setting.

Each patient who was misdiagnosed by radionuclide ventriculography and referred for coronary bypass surgery had ischaemia at maximum exercise as shown by angina, ST depression, raised left ventricular filling pressure, or a combination of these indicators. The response of left ventricular ejection

fraction to exercise was reported to be 53%–89% sensitive and 49%–100% specific for coronary disease.^{1–3} Because of these wide ranges “generally accepted experience” is not easy to define. As we pointed out in our paper, the figures for sensitivity and specificity primarily depend upon the research design. We would like to focus on one methodological standard that is hardly ever adhered to in comparable studies. That is the avoidance of a post-test referral bias which occurs if the outcome of the exercise test influences a patient’s likelihood of undergoing coronary angiography and thus of being included in the study. Preferential selection of positive test responders will increase the apparent disease frequency and will result in a falsely low specificity and falsely high sensitivity. To our knowledge there is no previous study on radionuclide ventriculography which meets this criterion and reports the number of eligible patients who refused to undergo coronary angiography and therefore had to be excluded. Adherence to this standard accounts for the low frequency of disease in our study group. We are unable to comment on the study design and the results cited by Dr Underwood because the paper he cites has not yet been published.

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Notices

Cardiovascular therapy

An International Symposium on Cardiovascular Therapy, organised by the Portuguese Society of Cardiology and sponsored by the Clinical Council of the International Society and Federation of Cardiology, the European Society of Cardiology, and its Working Group on Cardiovascular Drug Therapy, will be held in Lisbon on 3 and 4 February 1986. Inquiries to: Professor Salomão S Amram, Portuguese Society of Cardiology, Campo Grande 28-4C, 1700 Lisbon, Portugal.

Fetal cardiovascular echography

A symposium of Current Status and Future Developments in Fetal Cardiovascular Echography will be held at Erasmus University, Rotterdam, on 25 and 26 April 1986. Further information from: Office for Post Graduate Medical Education, Erasmus University Rotterdam, POB 1738, 3000 DR Rotterdam, The Netherlands.

British Cardiac Society

The Annual General Meeting for 1986 will take place in York on 2 and 3 April 1986, and the closing date for receipt of abstracts will be 2 January 1986.

Checking of references

The British Heart Journal has been able to provide a reference-checking service but can no longer do so; other journals had ceased to offer this many years ago. In future authors should take great care to check at source any reference they cite, or confirm references previously filed by using Index Medicus rather than the published work of another author, which may perpetuate errors.

Exercise and arrhythmias

A symposium on exercise in the diagnosis and evaluation of treatment of arrhythmias, arranged jointly by the working group on exercise physiology and the working group on arrhythmias and electrophysiology of the European Society of Cardiology with the Hellenic Cardiological Society, will be held in Athens on 17 to 19 April 1986. Further information may be obtained from: Professor D V Cokkinos, Cardiology Department, Tzanio State Hospital, 5 Dorylaïou Street, 115 21 Athens, Greece.

Cardiac pacing and electrophysiology

The VIIIth World Symposium on Cardiac Pacing and Electrophysiology will be held in Jerusalem on 7 to 11 June 1987. Inquiries to: Dr S Feldman, c/o Secretariat, PO Box 50006, Tel Aviv 61500, Israel.

AUTHOR INDEX

1985, Volume 54

- ABDULLAH M *see* Ribeiro P *et al*
 ABELA G S *see* French *et al*
 ABITBOL G *see* Veyrat C *et al*
 ABLETT M B *see* Halsey C D J & Ablett M B
 ABRAHAMSEN A M *see* Rønnevik P K *et al*
 ADAM W E *see* Wichhammer S *et al*
 AGARWAL A K (& Lochan R G, Beard D, Redding V J) Efficacy of flecainide in the control of ventricular response during exercise in established atrial fibrillation in digitalised patients: its comparison with beta blockade 611 P
 AL FAGIH M *see* Ribeiro P *et al*
 AL-RUPAIE H K *see* Quyyumi A A *et al*
 AL ZAIBAG M *see* Ribeiro P *et al*
 ALBERS C *see* Odenmuyse O *et al*
 Peart I *et al*
 ALLAN L D (& Crawford D C, Anderson R H, Tynan M) Spectrum of congenital heart disease detected echocardiographically in prenatal life 523
 — (& Crawford D C, Chitt S K, Anderson R H, Tynan M J) The familial recurrence of congenital heart disease 613 P
 — (& Crawford D C, Tynan M J) Pulmonary atresia in prenatal life 640 P
 ALTMAN D I (& Murray J, Milner S, Dansky R, Levin S E) Asymmetric septal hypertrophy and hypothyroidism in children 533
 AMENDER I (& Seegers A, Simon R, Hetzer R, Lichtlen P R) Functional correlates of cardiac rejection from intramyocardial markers 653 P
 AMBUR A *see* Veyrat C *et al*
 AMLE J P *see* Ihlen H *et al*
 ANDERSON R H (& Becker A E) Pathways of preferential arterial conduction: correspondence 226
 — *see also* Allan L D *et al*
 Hegerty A S *et al*
 ANGELINI G L (& Passani S P, Breckenridge I M) Prostacyclin production in saphenous vein from patients receiving aspirin 636 P
 APPLETON D *see* Peart I *et al*
 ARNIM T VON *see* Von Arnim T
 ARNOLDA L *see* McGrath B P *et al*
 ARTMAN M F *see* Parrish M D *et al*
 AUSTIN A *see* Peart I *et al*
 BAANDRUP U *see* Ibsen H H W *et al*
 BAER F *see* Verbeugt F W A *et al*
 BAKER E J *see* Reidy J F *et al*
 BALARAM U S V (& Karas S, Halliday-Smith K A) Idiopathic infantile hypercalcaemia (Williams-Beuren syndrome) and associated cardiac anomalies: a clinical and echocardiographic study 652 P
 BALCON R *see* Greenbaum R A & Balcon R
 Murray N *et al*
 BALDWIN J C *see* McGregor C G A *et al*
 BALL S G *see* Cleland J G F *et al*
 BALLANTYNE D *see* Northcote R J *et al*
 BANIM S O *see* Dymond D S *et al*
 BARBER P V *see* Schofield P M *et al*
 BARBER R *see* Taylor N C *et al*
 BARBER R W *see* Ormerod O J M *et al*
 Stone D L *et al*
 BARNABY P F *see* Brown M A *et al*
 BATES D *see* Shaw P J *et al*
 BEARD D *see* Agarwal A K *et al*
 BECKER A E *see* Anderson R H & Becker A E
 Stewart P A *et al*
 BECKETT J *see* Fessatidis I *et al*
 BEEN M (& Kean D, Smith M A, Douglas R H B, Best J J K, Muir A L) Nuclear magnetic resonance in hypertrophic cardiomyopathy 48
 BELDER M DE *see* de Belder M
 BENNETT D H *see* Molajo A O & Bennett D H
 Molajo A O *et al*
 Schofield P M *et al*
 BENTALL H *see* Hackett D *et al*
 BENTALL H H *see* Fessatidis I Th *et al*
 BERNADET P *see* Douste-Blazy P *et al*
 BEST J J K *see* Been M *et al*
 BIASUCCI L M *see* Rebuzzi A G *et al*
 BING R F *see* Heagerty A M *et al*
 BLANCQUAERT A DEVLOO- *see* Devloo-Blancquaert A
 BLAZYP DOUSTE- *see* Douste-Blazy P
 BOUCEK R J *see* Parrish M D *et al*
 BOUISOUS H *see* Douste-Blazy P *et al*
 BOWEN R J *see* Schofield P M *et al*
 BOWKER T J (& Cross F W, Rumsby P T, Gower M C, Poole-Wilson P A, Fox K M, Bown S G, Rickards A F) Is localised intracoronary hyperkalaemia a risk of laser angioplasty? 637 P: Which ultraviolet laser wavelengths are selective for atheromatous as opposed to normal arterial wall? 635 P
 — (& Fox K M, Poole-Wilson P A, Bown S G, Rickards A F) Acute and chronic angiographic effects of in vivo coronary laser angioplasty 634 P
 BOWN S G *see* Bowker T J *et al*
 BOYD E G (& Holt P M, Sowton E) A modified energy delivery system for lower energy ablation 651 P
 BOYLE D MCC *see* Higginson J D S *et al*
 BRAIMBRIDGE M V *see* Saldanha C B R *et al*
 BRANDT P W *see* Brown M A *et al*
 BRANGENBERG R *see* Weil J *et al*
 BRANNAN J J *see* Fessatidis I *et al*
 BRECKENRIDGE I M *see* Angelini G D *et al*
 BRENAHAN J F *see* Sugrue D D *et al*
 BRITISH CARDIAC SOCIETY Autumn meeting, London, November 1985, proceedings 609
 BROCK T H CLUTTON- *see* Clutton-Brock T H
 BROOKS N *see* Kay P H *et al*
 BROWER R W (& Fioretti P, Simoons M, Haalebos M, Rulf E N R, Hugenholz P G) Surgical versus non-surgical management of patients soon after acute myocardial infarction 460
 BROWN M *see* McEwan J *et al*
 BROWN M A (& Norris R M, Barnaby P F, Geary G G, Brandt P W) Effect of early treatment with propranolol on left ventricular function four weeks after myocardial infarction 351
 BUCKNELL C A *see* Lewis S *et al*
 BUGIARDINI R (& Ferrini D, Galvani M, Gridelli C, Pozzati A, Puddu P, Lenzi S) Effects of vasodilators on exercise capacity and myocardial oxygen supply in patients with angina pectoris and normal coronary arteries 610 P
 BUHLMAYER K *see* Weil J *et al*
 BUTICK B *see* Higginson J D S *et al*
 BULL C *see* Sullivan I D *et al*
 BUN-TAN L B *see* Ribeiro P *et al*
 BUNTON R W (& Shore D F, Keeton B R, Sutherland G R, Monro

- J L) The management of interrupted aortic arch 625 P
- BURGER J *see* Parrish M D *et al*
- BURTON R W (& Jones R A, Lang P, Castaneda A R) Anomalous origin of left coronary artery from pulmonary artery: ligation versus establishment of a two coronary system 624 P
- BUSH A (& Busst C, Shinebourne E A) Does epoprostenol (prostaglandin) enhance the selective pulmonary vasodilator effect of oxygen in children with congenital heart disease? 625 P
- BUSST C *see* Bush A *et al*
- BUTROUS G S (& Davies D W, Debbas N, Erwin J, Camm A J) The clinical significance of ventricular supernormal period in man 641 P
- BUYZERE M *de see* De Buyzere M
- CABRERA A (& Galdeano J, Lekuona I) Persistent left sided fifth aortic arch in a neonate: case report 105
- CALDER A L *see* Neutze J M *et al*
- CAMM A J *see* Butrous G S *et al*
- CAMPBELL R W F *see* Wren C *et al*
- CAMPBELL T J (& Gavaghan T P, Morgan J J) Intravenous sotalol for the treatment of atrial fibrillation and flutter after cardiopulmonary bypass. Comparison with disopyramide and digoxin in a randomised trial 86
- CANNING G *see* Northcote R J *et al*
- CAPLIN J L *see* Dymond D S *et al*
- CARRERAS F (& Thwaites B C, Castle G, Shapiro L, Donaldson R) Pitfalls in the comparison of Doppler estimates of aortic flow velocities with cardiac catheterisation data 649 P
- *see also* Thwaites B C *et al*
- CARTLIDGE N E F *see* Shaw P J *et al*
- CASTANEDA A R *see* Burton R W *et al*
- CASTLE G *see* Carreras F *et al*
- CATTERALL J R *see* Stewart P M & Catterall J R
- CELLIERS C P *see* Gordon N F *et al*
- CHALLENGER V *see* Upward J *et al*
- CHAMBERLAIN D A Digitalis, where are we now? editorial 227
- *see also* Lewis S *et al*
- CHESMAN M G (& Mehta D, Walker J, Redding V J) Severe left main stem stenosis: safety of discharge home to await elective surgery 631 P
- CHIERCHIA S *see* Hackett D *et al*
- CHILD A *see* Handler C B *et al*
- CHITA S K *see* Allan L D *et al*
- CHOPRA P *see* Mukhopadhyay A K & Chopra P
- CHILLIERS J F *see* Gordon N F *et al*
- CLARK D L *see* Rees M R *et al*
- CLARKE L M *see* Papouchado M *et al*
- CLARKSON P M *see* Neutze J M *et al*
- CLELAND J (& Dargie H J, Findlay I, Wilson J) Effect of amiodarone on arrhythmia and left ventricular function in heart failure 647 P
- (& Gillen G, Dargie H J, Robertson J I S) Effects of enalapril on renal function in heart failure 655 P
- *see also* Hamilton J R L *et al*
- CLELAND J G F (& Dargie H J, Ball S G, Gillen G, Hodsman G P, Morton J J, East B W, Robertson I, Ford I, Robertson J I S) Effects of enalapril in heart failure. a double blind study of effects on exercise performance, renal function, hormones, and metabolic state 305
- CLEMENT D *see* Scheerder I *et al*
- CLEMENT D L *see* Jordans L *et al*
- CLUTTON-BROCK T H *see* Cooper T J *et al*
- COBBE S M (& Manley B S) Contrasting effects of the class III agents amiodarone and sotalol in ischaemic myocardium 645 P
- COCKROFT J *see* Petri M P *et al*
- COLEMAN E N *see* Houston A B *et al*
- CONTI C R *see* Fenech A *et al*
- CONWAY N *see* Keenan D J M *et al*
- COOKE J *see* O'Callaghan C *et al*
- COOPER T J (& Clutton-Brock T H, Jones S N, Tinker J, Treasure T) Factors relating to the development of hypertension after cardiopulmonary bypass 91
- CONROY R *see* Daly L *et al*
- CORNIL A *see* Kostucki W *et al*
- CORR L *see* Dollery C T & Corr L
- COSTA D C *see* Walton S *et al*
- COWLEY A J (& Stamer K, Rowley J M, Hampton J R) Double blind comparison of the effect of increasing diuretics or adding captopril in the treatment of moderate cardiac failure 638 P
- CRANE T (& Westgate C, Shapiro L M) Inappropriate left ventricular hypertrophy in mild hypertension: echocardiographic study in middle aged subjects 649 P
- *see also* Quyyumi A A *et al*
- CRAWFORD D C *see* Allan L D *et al*
- CREA F *see* Fenech A *et al*
- CRICHTON E *see* Shaw T R D *et al*
- CRICK J C P Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia: correspondence 550
- Reverse delta wave: a reliable sign of impending ventricular fibrillation in right coronary angiography 645 P
- (& Davies D W, Holt P, Curry P V L, Sowton E) Effect of exercise on ventricular response to atrial fibrillation in Wolff-Parkinson-White syndrome 80
- *see also* Polydorou A *et al*
- CROSS F W *see* Bowker T J *et al*
- CROSSLAND P *see* Taylor N C *et al*
- CUMBERLAND D *see* Shiu M F *et al*
- CUNNINGHAM A D *see* Rowland E *et al*
- CURRY P V L *see* Crick J C P *et al*
- DALEY P J (& Sagar K B, Wann L S) Doppler echocardiographic measurement of flow velocity in the ascending aorta during supine and upright exercise 562
- DALY K *see* Timmis A D *et al*
- DALY L (& Conroy R, Hickey N, Mulcahy R) Natural history of post-myocardial infarction angina pectoris 610 P
- DANDONA P *see* Symons C *et al*
- DANSKY R *see* Altman D I *et al*
- DARGIE H J *see* Cleland J *et al*
- DARGIE H J *see* Cleland J G F *et al*
- DARGIE H J *see* Findlay I *et al*
- DARGIE H J *see* Fisher B M *et al*
- DARGIE H J *see* McLennan J *et al*
- DAVIES D W (Wainwright R J, Tooley M, Camm A J) Automatic diagnosis of ventricular tachycardia by new methods of electrogram analysis 641 P
- *see also* Butrous G S *et al*
- DAVIES D W *see* Crick J C P *et al*
- DAVIES G *see* Hackett D *et al*
- DAVIES M J (& Thomas A C) Intramyocardial platelet emboli in unstable angina and sudden ischaemic death 636 P
- *see also* Dawkins K D *et al*
- DAVIES J R *see* Shaw T R D *et al*
- DAWKINS K D (& Wilson A G, Thomas A C, Davies M J) Post-mortem coronary arteriography following sudden death 611 P
- DAWSON J R (& Gibson D G) Functional effects of regional left ventricular asynchrony during acute angina 621 P
- (& Thompson D S, Signy M, Juul S M, Turnbull P, Jenkins B S, Webb-Peploe M M) Acute haemodynamic and metabolic effects of dopexamine, a new dopaminergic receptor agonist, in patients with chronic heart failure 313
- DE BELDER M *see* Pumphrey C W *et al*
- DE BUYZERE M *see* De Scheerder I *et al*

- DE GRAEVE J *see* Douste-Blazy P *et al*
 DE LEVAL M (& Stark J, Karl T, Taylor J F N) Surgical treatment of absent pulmonary valve syndrome 629 P
 DE SCHIEERDER I (& De Buyzere M, Clement D) Association between post-pericardiotomy syndrome and coronary occlusion after aortic valve replacement case report 445
 DE ZWAAN C *see* Verheugt F W A *et al*
 DEANFIELD J *see* McKenna W J *et al*
 DEANFIELD J E *see* Ortiz E *et al*
 Sullivan I D *et al*
 DEBRAS N *see* Butrous G S *et al*
 DEL TORO S (& Kelly M J, Kalff V, Stellin G, Mee R B B, Venables A W) Non-invasive assessment of pulmonary blood supply after staged repair of pulmonary atresia 209
 DELAGARDELLE C *see* Wieselhammer S *et al*
 DELLBORG M (& Held P, Swedberg K, Vedin A) Rupture of the myocardium Occurrence and risk factors 11
 DENNIS A R (& Richards D A, Ross D L, Uther J B) Comparison of prognostic significance of delayed potentials and inducible ventricular tachycardia in 306 survivors of acute myocardial infarction 609 P
 DEVLOO-BLANQUAERT A *see* van Egmond H *et al*
 DICKINSON S *see* McKenna W J *et al*
 Stockins B *et al*
 DICKINSON D F *see* Goldberg S J *et al*
 DION R *see* Kujer P *et al*
 DOHLEMAN C *see* Weil J *et al*
 DOIG W B *see* Houston A B *et al*
 DOLLERY C T (& Corr L) Drug treatment of heart failure 234
 DONALDSON R *see* Carreras F *et al*
 Shapiro L M *et al*
 Thwaites B C *et al*
 DORRANCE D E *see* Handler C E *et al*
 DOUGLAS R H B *see* Been M *et al*
 DOUSTE-BLAZY P (& Thiers J C, Valdigue P, Bouissou H, de Graeve J, Bernadet P) Skin apolipoprotein B values in normocholesterolaemic patients with coronary artery disease: a discriminatory test: correspondence 452
 DRUMMOND L *see* Sutherland G R *et al*
 DUNCAN F M *see* Shaw T R D *et al*
 DYMOND D S (& Caplin J L, O'Keefe J C, Flatman W D, Banim S O) Attenuation by calcium blockade of the abnormal response to cold pressor stimulation in patients with ischaemia and normal coronary arteries 637 P
 DYSZKIEWICZ W *see* Zerbe F *et al*
 DZIBIELEWSKI T *see* Zerbe F *et al*
 EAST B W *see* Cleland J G F *et al*
 EDELMANN B *see* von Essen R *et al*
 EDWARDS C R W *see* Shaw T R D *et al*
 ERNIG M J *see* van Ernig M J
 EFFERT S *see* von Essen R *et al*
 EGMOND H *see* van Egmond H
 EKROTH R (& Thompson R, Jackson A, Lincoln C) Does elective hypothermic circulatory arrest cause brain damage? Influence of its duration and other perioperative variables in patients with congenital heart disease 640 P
 EL-SAYED H *see* Miller G A H *et al*
 ELL P J *see* Smith P L C *et al*
 Walton S *et al*
 EMANUEL R *see* Hayward R *et al*
 EMANUEL R W *see* Walton S *et al*
 ENGLISH T A H *see* Taylor N C *et al*
 ERWIN J (& McWilliams E, Gearty G, Maurer B) Haemodynamic and symptomatic improvement using dual chamber pacing in hypertrophic cardiomyopathy 641 P
 — *see also* Butrous G S *et al*
 ESPINER E A *see* Stewart D B *et al*
 ESSEN R *see* von Essen R
 EVANS R *see* Linker N J *et al*
 FAGHI M A L *see* Al Fagh M
 FAILLACE R T (& Greenland P, Nanda N C) Rapid expansion of a saccular aneurysm on the left coronary sinus of Valsalva: a role for early surgical repair: case report 442
 FARAH S *see* Ribeiro P *et al*
 FERRING A *see* Rees M R *et al*
 FENECH A (& Crea F, Conti C R, Abela G S) Argon laser recanalisation of acutely thrombosed coronary arteries in live dogs 628 P
 FERRINI D *see* Bugiardini R *et al*
 FESSATIDIS I (& Man W K, Becket J, Brannan J J, Taylor K M) Epoprostenol (prostacyclin) therapy during cardiac surgery—is it beneficial? 629 P
 — *see also* Hackett D *et al*
 FESSATIDIS I Th (& Hackell D R, Oakley C, Sapsford R N, Bental H H) Ten years clinical evaluation of models 6400 and 6120 Starr-Edwards isolated mitral valve replacement 638 P
 FINDLAY I (& Henderson E, Taylor R, Grant S, Dargie H J) Cardiovascular fitness improves the coronary risk profile 656 P
 — *see also* Cleland J *et al*
 FIORETTI P *see* Brower R W *et al*
 FIRMIN D N *see* Rees M R *et al*
 Underwood S R *et al*
 FISHER B M (& Dargie H J, Gillen G, Henderson E, Frier B M) Impairment of left ventricular function in diabetics—evidence for a specific heart muscle disease 656 P
 FLATMAN W D *see* Dymond D S *et al*
 FOALE R A *see* Nihoyannopoulos P *et al*
 Ribeiro P *et al*
 FORD I *see* Cleland J G F *et al*
 FORFANG K *see* Ihlen H *et al*
 FORPAR J C (& Godman M J) Functional and anatomical correlates in atrial septal defect: an echocardiographic analysis 193
 FORTUNE F *see* Symons C *et al*
 FOX K M *see* Bowker T J *et al*
 Levy R D *et al*
 Quyyumi A A *et al*
 Rees M R *et al*
 Underwood S R *et al*
 FRANKLIN R *see* McKenna W J *et al*
 Ortiz E *et al*
 FREEMAN L J (& Nixon P G F) Reoperation for angina after previous aortocoronary bypass surgery: correspondence 552
 FRIER B M *see* Fisher B M *et al*
 FRUSTACI A (& Loperfido F, Pennestri F) Hypertrophic cardiomyopathy simulating an infiltrative myocardial disease: case report 329
 FUKAMI K *see* Ogawa H *et al*
 GALDEANO J *see* Cabrera A *et al*
 GALVANI M *see* Bugiardini R *et al*
 GAVAGHAN T P *see* Campbell T J *et al*
 GEARTY G *see* Erwin J *et al*
 GEARTY G G *see* Brown M A *et al*
 GEN C GUANG- *see* Guang-Gen C
 GIBBS J L Echocardiography and ambulatory electrocardiography in patients with tuberculous sclerosis 653 P
 — The heart and tuberculous sclerosis. An echocardiographic and electrocardiographic study 596
 — (& Qureshi S A, Radley-Smith R, Yacoub M H) Doppler echocardiography following anatomical correction of transposition of the great arteries 652 P
 GIBSON C J (& Laird B E, Williams B D, Rajathurai A, Mitra B, Rankin D) New technique for showing the relation of tomographic myocardial perfusion images obtained with thallium-201 to the coronary arteries 367
 GIBSON D *see* Lincoln C *et al*
 GIBSON D G *see* Dawson J R & Gibson D G
 GILLEN G *see* Cleland J *et al*
 Cleland J G F *et al*
 Fisher B M *et al*

- GLOVER D R (& Lintler W A) Factors influencing survival and mode of death in chronic ischaemic cardiac failure 613 P
- GODMAN M J *see* Forfar J C & Godman M J
- GOLD R G Do we need a new standard for electrocardiographs? editorial 119
- GOLDBERG S J (& Dickinson D F, Wilson N) Evaluation of an elliptical area technique for calculating mitral blood flow by Doppler echocardiography 68
- GOODWIN J F The challenge and the reproach of infective endocarditis: editorial 115
- GORDON N F (& van Rensburg J P, Russell H M S, Kawalsky D L, Celliers C P, Cilliers J F, Myburgh D P) Effect of beta₁ selective adrenoceptor blockade on physiological response to exercise 96
- GOTO Y *see* Ogawa H *et al*
- GOWER M C *see* Bowker T J *et al*
- GRAEVE J DE *see* De Graeve J
- GRAFF R F *see* Radford D J *et al*
- GRAHAM T P *see* Parrish M D *et al*
- GRANT S *see* Findlay I *et al*
- GREENBAUM R A (& Balcon R) Eleven years' experience of pacemaker insertion and therapy in a cardiothoracic centre 615 P
—*see also* Symons C *et al*
- GREENLAND P *see* Faillace R T *et al*
- GRIDELLI C *see* Bugiardini R *et al*
- GRIFFIN B *see* Timmis A D *et al*
- GUANG-GEN C *see* Lu-Li S *et al*
- GUINN G A *see* Hallim M A *et al*
- GUNDERSEN T *see* Rennevik P K *et al*
- GWILT D J (& Petri M, Lewis P W, Nattrass M, Pentecost B L) Myocardial infarct size and mortality in diabetic patients 466
- HAALBOS M *see* Brower R W *et al*
- HACKETT D (& Davies G, Chierchia S, Masci A) Effect of nitrates on coronary re-occlusion during intracoronary thrombolysis 619 P
- HACKETT D (& Fessatides I, Sapsford R, Bentall H, Oakley C) Long term evaluation of isolated Starr-Edwards aortic valve replacement 629 P
- HACKETT D R *see* Fessatidis I Th *et al*
- HALLIM M A (& Mercer E N, Guinn G A) Myocardial tuberculoma with rupture and pseudoaneurysm formation—successful surgical treatment: case report 603
- HALL R *see* Odemuyiwa O *et al*
- HALL R J C *see* Peart I *et al*
- HALLIDIE-SMITH K A *see* Balaram U S V *et al*
- HAMERLYNCK R *see* Jordaens L *et al*
- HAMILTON I *see* Parker J *et al*
- HAMILTON J R L (& Cleland J, O'Kane H O J) Emergency surgery following percutaneous transluminal coronary angioplasty 634 P
—(& Mulholland H C, Cleland J) Chylopericardium: a rare complication of a Waterston shunt: case report 548
- HAMPTON J R *see* Cowley A J *et al*
- HANDLER C E (& Child A, Light N D, Dorrance D E) Mitral valve prolapse, aortic compliance, and skin collagen in joint hypermobility syndrome 501
—(& Sowton E) Exercise induced ST elevation post-infarction: prognostic importance and relation to site of infarct 646 P
- HANSEN O K *see* Vesterlund T *et al*
- HARRISON M J G *see* Smith P L C *et al*
- HARTNELL G G (& Parnell B M, Pridie R B) Coronary artery ectasia. Its prevalence and clinical significance in 4993 patients 392
- HATLE L *see* Hegrenas L & Hatle L
- HAUGE S NITTER *see* Nitter-Hauge S
- HAWKEY C *see* Pearce P C *et al*
- HAWORTH S G Lung biopsied in different types of congenital heart disease. computer-assisted structural and functional correlations 625 P
- HAYWARD R (& Hunter G J S) Digital subtraction angiography in coronary artery bypass graft assessment: clinical applicability 357
—(Swanton H, Emanuel R) Coronary blood transit: effects of nifedipine assessed by parametric digital subtraction angiography 650 P
- HAYWOOD G A *see* Joy M *et al*
- HAZE K *see* Ogawa H *et al*
- HEAGERTY A M (& Ollerenshaw J D, Jackson J, Bing R F, Thurston H, Swales J D) Linoleic acid, leucocyte sodium transport, free calcium, and blood pressure 635 P
- HEALY M J R *see* Mulrow J P *et al*
- HEARSE D J *see* Saldanha C B R *et al*
- HEAVISIDE D W *see* Shaw P J *et al*
- HECK I *see* Reska S N *et al*
- HEDDLE W F (& Jones M E, Tonkin A M) Sinus node sequences after atrial stimulation: similarities of effects of different methods 568
- HEGERTY A S (& Anderson R H, Ho S Y) Congenital heart malformations in the first year of life—a necropsy study 583
- HEGRENAS L (& Hatle L) Aortic stenosis in adults, non-invasive estimation of pressure differences by continuous wave Doppler echocardiography 396
- HELD P *see* Dellborg M *et al*
- HENDERSON E *see* Findlay I *et al*
Fisher B M *et al*
McLenachan J *et al*
- HENZE E *see* Wicshammer S *et al*
- HERSHKO C *see* Kramer M R *et al*
- HESS M L Cardiac transplantation: correspondence 555
- HETZER R *see* Amende I *et al*
- HICKEY N *see* Daly L *et al*
- HIGGINS J D S (& McCann J P, McHugh B, Buick B, Boyle D McC) Effect of chronic amiodarone treatment on pulmonary function 612 P
- HIRAMORI K *see* Ogawa H *et al*
- HO S Y *see* Hegerty A S *et al*
- HODSMAN G P *see* Cleland J G F *et al*
- HOFLING B *see* von Arnim T *et al*
- HOOGENHUYZE D C A VAN *see* VAN Hoogenhuyze D C A
- HOLLMAN A Plants and cardiac glycosides 258
- HOLMES D R *see* Sugrue D D *et al*
- HOLT P *see* Crick J C P *et al*
- HOLT P M *see* Boyd E G *et al*
- HONEY M *see* Muller G A H *et al*
- HOUSTON A B (& Simpson I A, Sheldon C D, Doig W B, Coleman E N) Doppler estimation of pressure gradients in infundibular pulmonary stenosis 618 P
—*see also* Simpson I A *et al*
- HUGENHOLTZ P G Is early recanalisation in acute myocardial infarction recommendable 636 P
—*see also* Brower R W *et al*
- HUNTER G *see* Hayward R *et al*
- HUNTER G J S *see* Hayward R & Hunter G J S
- HUNTER S *see* Wren C *et al*
- HUSSAIN S *see* Skehan J D *et al*
- HUTTON I *see* McGhie I *et al*
Simpson I A *et al*
Tan L B *et al*
Tweddel A *et al*
- IBSEN H H W (& Baandrup U, Simonsen E E) Familial right ventricular dilated cardiomyopathy 156
- ILHEN H (& Myhre E, Amhe J P, Forfang K, Larsen S) Changes in left ventricular stroke volume measured by Doppler echocardiography 378
—*see also* Zhang Y *et al*
- IKEDA M *see* Ogawa H *et al*
- IKRAM H *see* Stewart D E *et al*
- IKRAM S *see* Lewis S *et al*
- ILLEY C D J (& Ablett M B) Percutaneous transluminal coronary angioplasty—results in patients with acute myocardial infarction 620 P
—Percutaneous transluminal coronary angioplasty—results in

- patients with multiple coronary stenoses 627 P
 ISHIKAWA T *see* Neutze J M *et al*
 ISLES C *see* McLennan J *et al*
- JACKSON A *see* Ekroth R *et al*
 JACKSON B *see* McGrath B P *et al*
 JACKSON J *see* Heagerty A M *et al*
 JAMES M A *see* Papouchado M *et al*
 JAMIESON S W *see* McGregor C G A *et al*
 JENKINS B S *see* Dawson J R *et al*
 JENNINGS G *see* McGrath B P *et al*
 JEWITT D E *see* Timmis A D *et al*
 Trosser A *et al*
 JOHNSON A M *see* Keenan D J M *et al*
 JOHNSTON C I *see* McGrath B P *et al*
 JONAS R A *see* Burton R W *et al*
 JONES D A *see* Lipkin D P *et al*
 JONES M E *see* Heddle W F *et al*
 JONES O *see* Ladusans E J *et al*
 JONES O D H *see* Reidy J F *et al*
 JONES S N *see* Cooper T J *et al*
 JORDAENS L (& Hamerlynck R, Clement D L) Efficacy of an implanted automatic defibrillator which had induced atrial fibrillation: case report 605
 JORDAN S C Two dimensional and pulsed Doppler investigations of children with early systolic murmurs 618 P
 JOSEPH M *see* Ladusans E J *et al*
 JOSEPH M C *see* Reidy J F *et al*
 JOSEPH P L A *see* Smith P L C *et al*
 JOY M (& Haywood G A, Webb-Peploe M M) Management of a case of refractory variant angina with benzhexol hydrochloride (trihexyphenidyl hydrochloride): case report 448
 JULIAN D G The practical implications of the coronary artery surgery trials: review 343
 — *see also* Shaw P J *et al*
 JUUL S M *see* Dawson J R *et al*
- KALFF V *see* del Torso S *et al*
 KALMANSON D *see* Veyrat C *et al*
 KARAS S *see* Balaram U S V *et al*
 KARL T *see* Leval M *et al*
 KAWALSKY D L *see* Gordon N F *et al*
 KAY P H (& Brooks N, Magee P, Sturridge M F, Walesby R K, Wright J E C) Bypass grafting to the right coronary artery with and without endarterectomy: patency at one year 489
 KEAN D *see* Been M *et al*
 KEENAN D J M (& Monro J L, Ross J K, Manners J M, Conway N, Johnson A M) Left ventricular aneurysm. The Wessex experience 269
 KEETON B R *see* Bunton R W *et al*
 Sutherland G R *et al*
 KEKWICK C A *see* Linker N J *et al*
 KELLY M J *see* del Torso S *et al*
 KERR I H *see* O'Callaghan C *et al*
 KHAN F *see* Trosser A *et al*
 KHOSLA T *see* Mir M A *et al*
 KIAT H *see* McGrath B P *et al*
 KINGSTON T *see* Schofield P M *et al*
 KITNEY R *see* Sichen J D *et al*
 KLIPSTEIN R H *see* Rees R S O *et al*
 Underwood S R *et al*
 KNOPP R *see* Reske S N *et al*
 KOSTUCKI W (& VAN Kuyk M, Cornil A) Changing echocardiographic features of a hydatid cyst of the heart: case report 224
 KRAMER M R (& Shilo S, Hershiko C) Atrioventricular and sinoatrial block in thyrotoxic crisis: case report 600
 KRIKLER D M Withering and the foxglove: the making of a myth 256
 — *see also* Savill J *et al*
- KRIKLER S *see* McKenna W J *et al*
 KROPP J *see* Reske S N *et al*
 KRUG H *see* Zerbe F *et al*
 KUBAT K *see* Sengers R C A *et al*
 KUIJER P (& Dion R, VAN Merrienboer F) Right atrial spleen: case report 337
 KUMPENG V *see* Robinson P J *et al*
 KUYK M VAN *see* VAN Kuyk M
- LADUSANS E J (& Tynan M, Joseph M, Jones O, Curry P V L) Multi-programmable pacemakers—essential for pacing in children 632 P
 LAIRD E E *see* Gibson C J *et al*
 LAKWIJK-VONDROVICOVA E VAN *see* VAN Lakwijk-Vondrovicova E
 LANE G E *see* Sugrue D D *et al*
 LANG P *see* Burton R W *et al*
 LANG R E *see* Weil J *et al*
 LARSEN S *see* Ihlen H *et al*
 LAVENDER J P *see* Stockins B *et al*
 LAYTON C Lead specificity of the maximum ST/heart rate slope response: correspondence 554
 — *see also* Murray N *et al*
 LEDDA R *see* Reske S N *et al*
 LEE W H *see* Packer M *et al*
 LEKUONA I *see* Cabrera A *et al*
 LENZI S *see* Bugiardini R *et al*
 LESSANA A *see* Veyrat C *et al*
 LEVAL M DE *see* de Leval M
 LEVIN S E *see* Altman D I *et al*
 LEVORSTAD K *see* Zhang Y *et al*
 LEVY R *see* Quyyumi A A *et al*
 LEVY R D (& Shapiro L M, Wright C, Mockus L, Fox K M) Ambulatory pulmonary artery pressure monitoring in the evaluation of angina pectoris 643 P
 — (& Shapiro L M, Mockus L, Wright C, Fox K M) The significance of painless ST segment depression assessed by ambulatory pulmonary artery pressure monitoring 623 P
 LEWIS P W *see* Gwilt D J *et al*
 LEWIS S (& Bucknell C A, Ikram S, Vincent R, Chamberlain D A) Temporary transvenous cardioversion for recurrent ventricular tachyarrhythmias 612 P
 LI S LU- *see* Lu-Li S
 LIAN L RU- *see* Ru-Lian L
 LICHTLEN P R *see* Amende I *et al*
 LIGHT N D *see* Handler C E *et al*
 LINCOLN C (& Rigby M, Shinebourne E, Gibson D) Anatomic correction for transposition and DORV—early and intermediate structural and functional considerations 639 P
 — *see also* Ekroth R *et al*
 LINKER N J (& Evans R, Kekwick C A, Shaw D B) Ischaemia and sinus node disease 612 P
 LIPKIN D P (& Jones D A, Round J M, Poole-Wilson P A) Maximal force, fibre type, and enzymatic activity in quadriceps of patients with severe heart failure: a mechanism for reduced exercise capacity 622 P
 — (& Perrins J, Poole-Wilson P A) Respiratory gas exchange in the assessment of patients with impaired ventricular function 321
 — (& Poole-Wilson P A) Origins of breathlessness in chronic heart failure 609 P
 LITTLER W A *see* Glover D R & Littler W A
 LOCHAN R G *see* Agarwal A K *et al*
 LONGMORE D B *see* Rees R S O *et al*
 Underwood S R *et al*
 LOPERIFIDO F *see* Frustaci A *et al*
 Rebuzzi A G *et al*
 LU-LI S (& Guang-Gen C, Ru-Lian L) Valve prolapse in Behçet's disease 100
 LYONS J *see* Murray N *et al*

- McCANN J P *see* Higginson J D S *et al*
 MACARTNEY F J *see* Ortiz E *et al*
 Robinson P J *et al*
 Sullivan I D *et al*
 McDONALD A *see* Skehan J D *et al*
 McEWAN J (& Chierchia S, Davies G, Stevenson J, Brown M, Maseri A, MacIntyre I) Coronary vasodilation by calcitonin gene related peptide 643 P
 McGHIE I (& Tweddel A, Martin W, Hutton I) Detection of coronary disease: a comparison between exercise technetium ventriculography and exercise thallium imaging 617 P
 — *see also* Tweddel A *et al*
 McGRATH B P (& Arnolda L, Matthews P G, Jackson B, Jennings G, Kiat H, Johnston C I) Controlled trial of enalapril in congestive cardiac failure 405
 MCGREGOR C G A (& Jameson S W, Stinson E B, Oyer P E, Reitz B A, Baldwin J C, Shumway N B) Heart-lung transplantation for Eisenmenger's syndrome 630 P
 McHUGH B *see* Higginson J D S *et al*
 MACINTYRE I *see* McEwan J *et al*
 McKENNA W J Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia: correspondence reply 550
 — (& Deansfield J, Franklin R, Krikler S, Dickie S) Arrhythmia in children and adolescents with hypertrophic cardiomyopathy incidence and relation to prognosis 632 P
 — (& Sugrue D D) Left ventricular gradients in hypertrophic cardiomyopathy: correspondence reply 113
 — *see also* Mulrow J P *et al*
 Stockins B *et al*
 McLENACHAN J (& Henderson E, Isles C, Dargie H J) Arrhythmias and left ventricular hypertrophy in essential hypertension 645 P
 McLEOD A A *see* Timmis A D *et al*
 MACMILLAN R M *see* Rees M R *et al*
 McWILLIAMS E *see* Erwin J *et al*
 MADSEN J K Ischaemic heart disease and prodromes of sudden cardiac death. Is it possible to identify high risk groups for sudden cardiac death? 27
 MAGEE P *see* Kay P H *et al*
 MAN W K *see* Feassatidis I *et al*
 MANLEY B S *see* Cobbe S M & Manley B S
 MANNERS J M *see* Keenan D J M *et al*
 MANSSELL M A *see* Morgan S H *et al*
 MARANHÃO V *see* Rees M R *et al*
 MARTIN W *see* McGhie I *et al*
 Tweddel A *et al*
 MASERI A *see* Hackett D *et al*
 McEwan J *et al*
 MASTENBROEK C Cultivation and breeding of *Digitalis lanata* in the Netherlands 262
 MATTERN H *see* Reske S N *et al*
 MATTHEWS P G *see* McGrath B P *et al*
 MATTHYS D *see* VAN Egmond H *et al*
 MAURER B *see* Erwin J *et al*
 MEDINA N *see* Packer M *et al*
 MEE R B B *see* del Torso S *et al*
 MEHTA D *see* Cheesman M G *et al*
 MEIER B Benign coronary perforation during percutaneous transluminal coronary angioplasty 33
 MERCER E N *see* Halim M A *et al*
 MERRIENBOER F VAN *see* VAN Merrienboer F
 MILLER G A H Balloon valvuloplasty and angioplasty in congenital heart disease 285
 — (& Honey M, El-Sayed H) Isolated coronary ostial stenosis—a previously unrecognised clinical syndrome 611 P
 MILLS P G *see* Pumphrey C W *et al*
 Skehan J D *et al*
 MILNER S *see* Altman D I *et al*
 MIR F *see* Mir M A *et al*
 MIR M A (& Mir F, Khosla T) Prevalence of hypertension in habitually salted-tea drinking population in Northern Kashmir 613 P
 MITCHELL A *see* Yusuf S *et al*
 MITCHELL A G (& Yacoub M H) Conduction between donor and recipient atria following orthotopic cardiac transplantation 615 P
 MITCHELL M *see* Savill J *et al*
 MITTRA B *see* Gibson C J *et al*
 MOCKUS L *see* Levy R D *et al*
 Quyyumi A A *et al*
 MOCKUS L J *see* Quyyumi A A *et al*
 MOLAJO A O (& Bennett D H) Effect of xamoterol (ICI 118587), a new beta₁ adrenoceptor partial agonist, on resting haemodynamic variables and exercise tolerance in patients with left ventricular dysfunction 17
 — (& Summers G D, Bennett D H) Effect of percutaneous transluminal coronary angioplasty on arrhythmias complicating angina 375
 MONAGHAN M *see* Timmis A D *et al*
 MONRO J L *see* Bunton R W *et al*
 Keenan D J M *et al*
 MORGAN J J *see* Campbell T J *et al*
 MORGAN S H (& Mansell M A, Thompson F D) Fluid removal by haemofiltration in diuretic resistant cardiac failure: case report 218
 MORTON J J *see* Cleland J G F *et al*
 MORTON P *see* O'Keefe D B *et al*
 MOSS D W *see* Ribeiro P *et al*
 MUIR A L *see* Been M *et al*
 MUKHOPADHAYAY A K (& Chopra P) Diffuse non-specific aortitis with multiple saccular aneurysms and aorto-enteric fistula: case report 102
 MULCAHY R *see* Daly L *et al*
 MULHOLLAND H C (& Shields M D) The assessment of surgical shunt patency by Doppler 639 P
 — *see also* Hamilton J R L *et al*
 MULROW J P (& Healy M J R, McKenna W J) Spontaneous variability of ventricular arrhythmia and its effect on the optimal duration of electrocardiographic monitoring required 644 P
 MURRAY J *see* Altman D I *et al*
 MURRAY M *see* Skehan J D *et al*
 MURRAY N (& Lyons J, Balcon R, Layton C) How many patients with myocardial infarction are suitable for thrombolysis? 620 P
 MURRAY R G *see* Tan L B *et al*
 MURTAGH J G *see* O'Keefe D B *et al*
 MYBURGH D P *see* Gordon N F *et al*
 MYHRE E *see* Ihlen H *et al*
 Zhang Y *et al*
 NAGLE R E *see* Petri M P *et al*
 NANDA N C *see* Faillace R T *et al*
 NATHAN A W (& Spurrel R A J, Camm A J) Low energy endocardial countershock for the treatment of ventricular tachycardia and fibrillation 615 P
 NATTRASS M *see* Gwilt D J *et al*
 NEILSON G H *see* Radford D J *et al*
 NEUTZE J M (& Ishikawa T, Clarkson P M, Calder A L) Assessment of pulmonary vascular resistance in patients with ventricular septal defect 633 P
 NEWMAN S P *see* Smith P L C *et al*
 NICHOLLS M G *see* Stewart D E *et al*
 NIHOYANNOPOULOS P (& Foale R A, Stockins B, Oakley C M) Sensitivity of echocardiography in infective endocarditis 648 P
 — *see also* Ribeiro P *et al*
 Stockins B *et al*
 NITTER-HAUGE S *see* Zhang Y *et al*
 NIXON P G F *see* Freeman L J & Nixon P G F
 NORRIS R M *see* Brown M A *et al*
 NORTHGOTE R J (& Canning G, San K-M, Ballantyne D) Lipo-

- protein profiles in veteran endurance athletes and age matched subjects with coronary artery disease and controls 647 P
- OAKLEY C *see* Fessatidis I Th *et al*
Hackett D *et al*
- OAKLEY C M Management of primary pulmonary hypertension: correspondence reply 554
— *see also* Nihoyannopoulos P *et al*
Rubeiro P *et al*
Stockins B *et al*
- OAKLEY D *see* Shiu M F *et al*
- O'CALLAGHAN C (& Cooke J, Kerr I H, Shinebourne B A) Subpulmonary pleural effusions in children after cardiac surgery 593
- ODEMUYIWA O (& Peart I, Albers C, Hall R) Reciprocal ST depression in acute myocardial infarction 479
- OGAWA H (& Hiramoto K, Haze K, Saito M, Sumiyoshi T, Fukami K, Goto Y, Ikeda M) Classification of non-Q-wave myocardial infarction according to electrocardiographic changes 473
- O'KANE H O J *see* Hamilton J R L *et al*
- O'KEEFE J C *see* Dymond D S *et al*
- O'KEEFE D B (& Morton P, Murtagh J G, Scott M E) Follow up to two years in 108 patients with severe early cardiac infarction treated with intravenous streptokinase 619 P
- OLIVER M F Strategies for preventing and screening for coronary heart disease: editorial 1
- OLLERENSHAW J D *see* Heagerty A M *et al*
- OLSEN E G J *see* Pearce P C *et al*
Quyyumi A A *et al*
Williams D G, Olsen E G J
- OREYE W *see* VAN Egmond H *et al*
- ORMEROD O J M (& Stone D L, Barber R W, Wraight E P, Petch M C) Assessment of ventricular function in aortic regurgitation by phase analysis of equilibrium radionuclide ventriculography 638 P
— *see also* Stone D L *et al*
- ORTIZ E (& Robinson P J, Deanfield J E, Franklin R, Macartney F J, Wyse R K H) Localisation of ventricular septal defects by simultaneous display of superimposed colour Doppler and cross sectional echocardiographic images 53
- OYER P E *see* McGregor C G A *et al*
- PACKER M (& Medina N, Yushak M, Lee W H) Usefulness of plasma renin activity in predicting haemodynamic and clinical responses and survival during long term converting enzyme inhibition in severe chronic heart failure. Experience in 100 consecutive patients 298
- PALMER R B G *see* Sanderson J E *et al*
- PAPOUCHADO M (& Walker P R, James M A, Clarke L M) The Mason-Likar "modified" exercise electrocardiograph: essentially identical to the 12 standard leads? 623 P
- PARKER J (& Hamilton I, Shepherd G) Clinical budgeting in cardiology and cardiac surgery 631 P
- PARNELL B M *see* Hartnell G G *et al*
- PARRISH M D (& Boucek R J, Burger J, Artman M F, Partain C L, Graham T P) Exercise radionuclide ventriculography in children: normal values for exercise variables and right and left ventricular function 509
- PARTAIN C L *see* Partain M D *et al*
- PASSANI S P *see* Angelini G D *et al*
- PEARCE P C (& Hawkey C, Symons C, Olsen E G J) Role of calcium in the induction of cardiac hypertrophy and myofibrillar disarray. Experimental studies of a possible cause of hypertrophic cardiomyopathy 420
- PEART I (& Albers C, Hall R J C) Exercise testing six weeks and 18 months after myocardial infarction in patients under 55 years 622 P
— (& Austin A, Appleton D, Hall R J C) Segmental wall motion analysis of cross sectional echocardiograms: its reproducibility and sources of variability 617 P
— *see also* Odemuyiwa O *et al*
- PEDOE H TUNSTALL- *see* Tunstall-Pedoe H
- PENNESTRI F *see* Frustaci A *et al*
- PENTECOST B L *see* Gwilt O J *et al*
- PEPLOE M M WEBB- *see* Webb-Peploe M M
- PERRINS J *see* Lipkin D P *et al*
- PERRY R A (& Shiu M F) Assessment of regional myocardial shortening using routine diagnostic coronary arteriograms 620 P
— (& Singh A, Shiu M F) Success and complication rates for coronary angioplasty in patients with and without previous myocardial infarction 634 P
- PETCH M C *see* Ormerod O J M *et al*
Stone D L *et al*
Taylor N C *et al*
- PETRI M *see* Gwilt D J *et al*
- PETRI M P (& Zeeulka A, Cockcroft J, Nagle R E) Potassium homeostasis following acute myocardial infarction—the effect of beta blockade 646 P
- PIDGEON J W Reoperation for angina after previous aortocoronary bypass surgery: correspondence reply 552
- PIEHLER J *see* Sugrue D D *et al*
- POLLOCK C Left ventricular gradients in hypertrophic cardiomyopathy. correspondence 113
- POLYDOROU A (& Crick J C P, Sowton E) How soon after PTCA should its results be assessed by exercise testing? 626 P
- PONIZYŃSKI A *see* Zerbe F *et al*
- POOLE-WILSON P A *see* Bowker T J *et al*
Lipkin D P & Poole-Wilson P A
Lipkin D P *et al*
Rees R S O *et al*
Underwood S R *et al*
- POZZATI A *see* Bugiardini R *et al*
- PRIDIE R B *see* Hartnell G G *et al*
- PUDDU P *see* Bugiardini R *et al*
- PUMPEREY C W (& Skehan D, de Belder M, Rothman M T, Mills P G) A comparison of exercise testing at ten days and three months after myocardial infarction: relation to the pattern of coronary disease 623 P
- QUARENDON P *see* Smith L D R & Quarendon P
- QURESHI S A *see* Gibbs J L *et al*
- QUYYUMI A A (& Al-Rufai H K, Olsen E G J, Fox K M) Coronary anatomy in patients with various manifestations of three vessel coronary artery disease 362
— (& Crake T, Wright C, Mockus L, Levy R, Fox K M) The effects of beta blocker, calcium antagonist, and nitrate in patients with exertional and rest angina 643 P
— (& Wright C M, Mockus L J, Fox K M) How important is a history of chest pain in determining the degree of ischaemia in patients with angina pectoris? 22
— (Mockus L J, Yacoub M, Fox K M) Effects of myocardial revascularisation in patients with effort angina and those with effort and nocturnal angina 557
- RADEMAKER M *see* Shaw T R D *et al*
- RADFORD D J (& Graff R F, Neilson G H) Diagnosis and natural history of Ebstein's anomaly 517
- RADLEY-SMITH R *see* Gibbs J L *et al*
- RAJATHURAI A *see* Gibson C J *et al*
- RANKIN D *see* Gibson C J *et al*
- RAO P S Descending aortography with balloon inflation. A technique for evaluating the size of persistent ductus arteriosus in infants with large proximal left to right shunts 527
- RAU G *see* von Essen R *et al*
- REBUZZI A G (& Loperfido F, Biasucci L M) Transient Q waves followed by left anterior fascicular block during exercise: case report 107
- REDDING V J *see* Agarwal A K *et al*
Cheseman M G *et al*
- REECE I J *see* Simpson I A *et al*

- REEDER G S *see* Sugrue D D *et al*
- RENSBURG J P *see* VAN Rensburg J P
- REES M R (& MacMillan R M, Reiter S, Rumberger H, Feiring A, Maranhao V, Clark D L) Sensitivity and specificity of coronary artery bypass graft patency estimation by cine computed tomography 655 P
- REES P G *see* Sullivan I D *et al*
- REES R S O (& Underwood S R, Savage P E, Klipstein R H, Firmin D N, Fox K M, Poole-Wilson P A, Longmore D B) Magnetic resonance assessment of left ventricular wall motion 650 P
- *see also* Underwood S R *et al*
- REIDY J F (& Jones O D H, Tynan M J, Baker E J, Joseph M C) Embolisation procedures in congenital heart disease 184
- REITER S *see* Rees M R *et al*
- REITZ B A *see* McGregor C G A *et al*
- REMMER P J *see* Verheugt F W A *et al*
- RES J C J *see* Verheugt F W A *et al*
- RESKE S N (& Heck I, Kropp J, Mattern H, Ledda R, Knopp R, Winkler C) Captopril mediated decrease of aortic regurgitation 415
- RIBEIRO P (& Al Zaibag M, Abdullah M, Salem C, Shea M J, Al Faghi M) Comparison of bioprosthesis degeneration in the aortic versus the mitral position 630 P
- (& Bun-Tan L B, Oakley C M) Management of aortic left ventricular tunnel: case report 333
- (& Nihoyannopoulos P, Farah S, Moss D W, Westaby S, Oakley C M, Foale R A) Role of transient ischaemia and perioperative myocardial infarction in the genesis of new septal wall motion abnormalities after coronary bypass surgery 140
- RICHARDS D A *see* Dennis A R *et al*
- RICKARDS A F *see* Bowker T J *et al*
- Rowland E *et al*
- RIGBY M *see* Lincoln C *et al*
- ROBERTSON I *see* Cleland J G F *et al*
- ROBERTSON J I S *see* Cleland J G F *et al*
- Cleland J G F *et al*
- ROBINSON P J (& Kumpeng V, Macartney F J) Cross sectional echocardiographic and angiographic correlation in criss cross hearts 61
- (& Wyse R K H, Macartney F J) Left ventricular outflow tract obstruction in complete transposition of the great arteries with intact ventricular septum. A cross sectional echocardiography study 201
- *see also* Ortiz E *et al*
- Sullivan I D *et al*
- RODGER J C *see* Simpson I A *et al*
- RØNNVEIK P K (& Gundersen T, Abrahamsen A M) Effect of smoking habits and timolol treatment on mortality and reinfarction in patients surviving acute myocardial infarction 134
- ROSS D L *see* Dennis A R *et al*
- ROSS J K *see* Keenan D J M *et al*
- ROTHMAN M *see* Skehan J D *et al*
- ROTHMAN M T *see* Pumphrey C W *et al*
- ROUND J M *see* Lipkin D P *et al*
- ROWLAND E (& Cunningham A D, Rickards A F) Adaptation of overdrive pacing rate for termination of AV re-entry tachycardia with change in posture—relevance for automatic software pacemakers 642 P
- ROWLEY J M *see* Cowley A J *et al*
- RU-LIAN L *see* Lu-Li S *et al*
- RUFIAIE H K AL- *see* Al-Rufiaie H K
- RUITENBEEK W *see* Sengers R C A *et al*
- RULF E N R *see* Brower R W *et al*
- RUMBERGER J *see* Rees M R *et al*
- RUMBSY P T *see* Bowker T J *et al*
- RUSSELL H M S *see* Gordon N F *et al*
- SAGAR K B *see* Daley P J *et al*
- SAITO M *see* Ogawa H *et al*
- SALDANHA C B R (& Braimbridge M V, Hearse D J) Do hyperkalaemic cardioplegic solutions damage vascular endothelium?—studies on vascular responsiveness in the rat heart 654 P
- SALEM C *see* Ribeiro P *et al*
- SAN K-M *see* Northcote R J *et al*
- SANDERSON J E (& Palmer R B G, Wright B Y) Myopotential sensing and DDD pacemakers 651 P
- SAPSFORD R *see* Hackett D *et al*
- Thompson G R, Sapsford R
- SAPSFORD R N *see* Feasatidis I Th *et al*
- SAVAGE P E *see* Rees R S O *et al*
- SAVILL J (& Mitchell M, Wood D, Krikler D M) Rapid plasma digoxin assay in outpatients—a useful routine technique? 248
- SAYED H EL- *see* El-Sayed H
- SCHREIBER I DE *see* De Scheerder I
- SCHMIDT W *see* VON Essen R *et al*
- SCHOFFIELD P M (& Barber P V, Kingston T) Preoperative and postoperative pulmonary function tests in patients with atrial septal defect and their relation to pulmonary artery pressure and pulmonary:systemic flow ratio 577
- (& Bowes R J, Bennett D H) Exercise capacity and heart rhythm following transvenous fulguration of atrioventricular conduction 614 P
- SCHREIBER M *see* VON Arnim T *et al*
- SCOTT M E *see* O'Keefe D B *et al*
- SEBENING W *see* Weil J *et al*
- SEEGERS A *see* Amende I *et al*
- SENGERS R C A (& Stadhouders A M, van Lakwijk-Vondrovicova E, Kubat K, Ruitenberg W) Hypertrophic cardiomyopathy associated with a mitochondrial myopathy of voluntary muscles and congenital cataract 543
- SERRUYS P W *see* Verheugt F W A *et al*
- SHAPIRO L *see* Carreras F *et al*
- Thwaites B C *et al*
- SHAPIRO L M (& Thwaites B, Westgate C, Donaldson R) Prevalence and clinical significance of aortic valve prolapse 179
- *see also* Crane T *et al*
- Levy R D *et al*
- SHAW D A *see* Shaw P J *et al*
- SHAW D B *see* Linker N J *et al*
- SHAW P J (& Bates D, Cartledge N E F, Heavyside D W, Shaw D A, Julian D G) Neurological complications of coronary artery bypass surgery 609 P
- SHAW T R D (& Duncan F M, Williams B C, Crichton E, Thomson S A, Davis J R E, Rademaker M, Edwards C R W) Plasma free captopril concentrations during short and long term treatment with oral captopril for heart failure 160
- SHEA M J *see* Ribeiro P *et al*
- SHELDON C D *see* Houston A B *et al*
- SHEPHERD G *see* Parker J *et al*
- SHIELDS M D *see* Mulholland H C & Shields M D
- SHILO S *see* Kramer M R *et al*
- SHINEBOURNE E *see* Lincoln C *et al*
- SHINEBOURNE E A *see* Bush A *et al*
- O'Callaghan C *et al*
- SHIU M F (& Sullivan N P, Oakley D, Cumberland D) Acute coronary occlusion during percutaneous transluminal coronary angioplasty 129
- (& Singh A) Spontaneous recanalisation of side branches occluded during percutaneous transluminal coronary angioplasty: case report 215
- *see also* Perry R A & Shiu M F
- Perry R A *et al*
- SHORE D F *see* Buntun R W *et al*
- SHUMWAY N B *see* McGregor C G A *et al*
- SIGEL H A *see* Wieshammer S *et al*
- SIGNY M *see* Dawson J R *et al*
- SILNY J *see* VON Essen R *et al*
- SILVERTON N P *see* Shiu M F *et al*
- SIMON R *see* Amende I *et al*

- SIMONSEN E E *see* Ibsen H H W *et al*
 SIMOONS M *see* Brower R W *et al*
 SIMOONS M L *see* Verheugt F W A *et al*
 SIMPSON I A (& Reece I J, Houston A B, Wheatley D J, Hutton I) Doppler ultrasound assessment of 155 patients with investigational bioprosthetic valve replacement 631 P
 —(& Rodger J C, Tweddel A C, Houston A B, Reece I J) Non-invasive haemodynamic assessment of mitral prosthetic function by Doppler ultrasound 648 P
 —*see also* Houston A B *et al*
 SINGH A *see* Perry R A *et al*
 Shu M F & Singh A
 SINGH R N (& Sosa J A) Coronary artery bypass grafting and hyperlipidaemia: correspondence 453
 SKEHAN J D (& Kiney R, Hussain S, Rothman M, McDonald A) Analysis of the signal averaged surface electrocardiogram for late potentials after myocardial infarction 642 P
 —(& Murray M, Mills P G) Infective endocarditis: current incidence and mortality 614 P
 SKEHAN D *see* Pumphrey C W *et al*
 SMITH H C *see* Sugrue D D *et al*
 SMITH K A HALLIDIE-*see* Hallidie-Smith K A
 SMITH L D R (& Quarendon P) Four dimensional cardiac imaging 616 P
 SMITH M A *see* Been M *et al*
 SMITH P L C (& Joseph P L A, Newman S P, Eli P J, Harrison M J G, Treasure T) Cerebral consequences of coronary artery surgery 630 P
 SMITH R RADLEY-*see* Radley-Smith R
 SMITH S A (& Weissberg P L, Tan L-B) Permanent pacemaker failure due to surgical emphysema: case report 220
 SMYTH P *see* Timmis A D *et al*
 SOMERVILLE J (& Warnes C) Transposition of the great arteries—adults and adolescents late after Mustard procedure 633 P
 —*see also* Warnes C A & Somerville J
 SOSA J A *see* Singh R N & Sosa J A
 SOUL F *see* Sutherland G R *et al*
 SOWTON E *see* Boyd E G *et al*
 Crick J C P *et al*
 Handler C B & Sowton E
 Polydorou A *et al*
 Timmis A D *et al*
 SPURRELL R A J *see* Nathan A W *et al*
 STADHOUDERS A M *see* Sengers R C A *et al*
 STAINER K *see* Cowley A J *et al*
 STARK J *see* de Leval M *et al*
 STAUCH M *see* Wieshammer S *et al*
 STELLIN G *see* del Torso S *et al*
 STEVENSON J *see* McEwan J *et al*
 STEWART D E (& Ikram H, Espiner E A, Nicholls M G) Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease 290
 STEWART P A (& Wladimiroff J W, Becker A E) Early prenatal detection of double outlet right ventricle by echocardiography: case report 340
 STEWART P M (& Catterall J R) Chronic nicotine ingestion and atrial fibrillation: case report 222
 STINSON E B *see* McGregor C G A *et al*
 STOCKINS B (& Dickie S, Lavender J P, Oakley C M, McKenna W J) Comparison of ejection dynamics in hypertrophic cardiomyopathy and valvular aortic stenosis 621 P
 —(& Dickie S, Nihoyannopoulos P, Lavender J P, McKenna W J, Oakley C M) Beneficial effect of beta blockade in aortic stenosis 655 P
 —*see also* Nihoyannopoulos P *et al*
 STONE D L (& Barber R W, Ormerod C J M, Petch M C, Wright E P) Quantification of intracardiac shunts by gold-195m, a new radionuclide with a short half life 495
 —*see also* Ormerod O J M *et al*
 STURRIDGE M F *see* Ray P H *et al*
 SUGRUE D D (& Holmes D R, Smith H C, Reeder G S, Lane G E, Vliestra R E, Bresnahan J F, Piehler J) Coronary artery thrombus as a risk factor for acute vessel occlusion during percutaneous transluminal coronary angioplasty: improving results 627 P
 —*see also* McKenna W J & Sugrue D D
 SULLIVAN I D (& Robinson P J, Macartney F J, Taylor J F N, Rees P G, Bull C, Deanfield J E) Percutaneous balloon valvuloplasty for pulmonary valve stenosis in infants and children 435
 SUMIYOSHI T *see* Ogawa H *et al*
 SUMMERS G D *see* Molajo A O *et al*
 SUTHERLAND G R (& Soul F, Keeton B R, Drummond L) The Doppler evaluation of discrete subvalvar and multilevel outflow tract obstruction in congenital heart disease 626 P
 —*see also* Bunton R W *et al*
 Upward J *et al*
 SWALES J D *see* Heagerty A M *et al*
 SWANTON H *see* Hayward R *et al*
 SWEDBERG K *see* Dellborg M *et al*
 SYMONS C (& Fortune F, Greenbaum R A, Dandona P) Cardiac hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism—an association 539
 —*see also* Pearce P C *et al*
 TAN L B (& Murray R G, Tweddel A C, Hutton I) Do cardiac glycosides exert positive inotropism in sinus rhythm? 654 P
 TAN L-B *see* Smith S A *et al*
 TAN L B BUN-*see* Bun-Tan L B
 TAYLER D I (& Vincent R) Artefactual ST segment abnormalities due to electrocardiograph design 121
 TAYLOR J F N *see* de Leval M *et al*
 Sullivan I D *et al*
 TAYLOR K M *see* Fessatidis I *et al*
 TAYLOR N C (& Barber R, Crossland P, Wraight E P, English T A H, Petch M C) Does left ventricular aneurysmectomy improve ventricular function in patients undergoing coronary bypass surgery? 145
 TAYLOR R *see* Findlay I *et al*
 THIERS J C *see* Douste-Blazy P *et al*
 THOMAS A C *see* Davies M J & Thomas A C
 Dawkins K D *et al*
 THOMPSON D S *see* Dawson J R *et al*
 THOMPSON F D *see* Morgan S H *et al*
 THOMPSON G R (& Sapsford R) Coronary artery bypass grafting and hyperlipidaemia: correspondence reply 453 P
 THOMPSON R *see* Ekroth R *et al*
 THOMSEN P E B *see* Vesterlund T *et al*
 THOMSON S A *see* Shaw T R D *et al*
 THURSTON H *see* Heagerty A M *et al*
 THWAITES B *see* Shapiro L M *et al*
 THWAITES B C (& Carreras F, Shapiro L, Castle G, Donaldson R) Assessment of pulmonary hypertension by two Doppler echocardiographic methods 650 P
 —*see also* Carreras F *et al*
 TIMMIS A D (& Crick J C P, Griffin B, Sowton E) Prevention of regional myocardial ischaemia during PTCA—the effects of infusing arterial blood 628 P
 —(& Griffin B, Crick J C P, Sowton E) The effects of early PTCA on the clinical course of unstable angina 627 P
 —(& Smyth P, Jewitt D E) Milrinone in heart failure. Effects on exercise haemodynamics during short term treatment 42
 —(& Monaghan M, Walker L, Daly K, McLeod A A, Jewitt D E) Milrinone in heart failure. Acute effects on left ventricular systolic function and myocardial metabolism 36
 TINKER J *see* Cooper T J *et al*
 TONKIN A M *see* Heddlie W F *et al*
 TOOLEY M *see* Davies D W *et al*
 TORO S DEL *see* del Torso S
 TREASURE T *see* Cooper T J *et al*
 Smith P L C *et al*

- TROSSER A (& Khan F, Jewitt D E) Evidence that flecainide is superior to disopyramide in suppressing chronic ventricular premature complexes 644 P
- TUNSTALL-PEDOE H Changing digoxin potency and cardiac mortality in England and Wales 1968-76 243
- TURNBULL P *see* Dawson J R *et al*
- TWEDDELL A (& Martin W, McGhie I, Hutton I) Is myocardial metabolism uniform? 648 P
- *see also* McGhie I *et al*
- TWEDDELL A C *see* Simpson I A *et al*
- Tan L B *et al*
- TYNAN M *see* Allan L D *et al*
- Ladusans E J *et al*
- TYNAN M J *see* Allan L D *et al*
- Reidy J F *et al*
- UEBIS R *see* VON Essen R *et al*
- UNDERWOOD S R Radionuclide ventriculography in coronary artery disease: correspondence 658
- (& Klipstein R H, Firmin D N, Fox K M, Poole-Wilson P A, Rees R S O, Longmore D B) Magnetic resonance quantification of atrial shunting and valvar regurgitation 616 P
- *see also* Rees R S O *et al*
- UPWARD J (& Challenor V, Sutherland G R) "Physiological" tricuspid and pulmonary regurgitation: their varying incidence in a representative adult cardiac population 618 P
- UTHER J B *see* Dennis A R *et al*
- VALDIGUIE P *see* Douste-Blazy P *et al*
- VAN EENIGE M J *see* Verheugt F W A *et al*
- VAN EGMOND H (& Oreye W, Matthys D, Verhaaren H, Devloo-Blanquaert A) Hypoplastic left heart syndrome and 45X karyotype 653 P
- VAN HOOGENHUYZE D C A *see* Verheugt F W A *et al*
- VAN KUYK M *see* Kostucki W *et al*
- VAN LAKWIJK-VONDROVICOVA E *see* Sengers R C A *et al*
- VAN MEERENBOER F *see* Kuijper P *et al*
- VAN RENSBURG J P *see* Gordon N F *et al*
- VEDIN A *see* Dellborg M *et al*
- VENABLES A W *see* del Torso S *et al*
- VERHAAREN H *see* VAN Egmond H *et al*
- VERHEUGT F W A (& VAN Eenige M J, Rees J C J, Simoons M L, Serruys P W, Vermeer F, VAN Hoogenhuyze D C A, Remme P J, de Zwaan C, Baer F) Bleeding complications of intracoronary fibrinolytic therapy in acute myocardial infarction. Assessment of risk in a randomised trial 455
- VERMEER F *see* Verheugt F W A *et al*
- VESTERLUND T (& Thomsen P E B, Hansen O K) Anomalous origin of the left coronary artery from the pulmonary artery in an adult: case report 110
- VEYRAT C (& Witchitz S, Lessana A, Ameur A, Abitbol G, Kalmanson D) Valvar prosthetic dysfunction. Localisation and evaluation of the dysfunction using the Doppler technique 273
- VINCENT R *see* Lewis S *et al*
- Tayler D I & Vincent R
- VLIETSTRA R E *see* Sugrue D D *et al*
- VON ARNIM T (& Höffing B, Schreiber M) Characteristics of episodes of ST elevation or ST depression during ambulatory monitoring in patients subsequently undergoing coronary angiography 484
- VON ESSEN R (& Schmidt W, Uebis R, Edelmann B, Effert S, Silny J, Rau G) Myocardial infarction and thrombolysis. Electrocardiographic short term and long term results using precordial mapping 6
- VONDROVICOVA E VAN LAKWIJK- *see* VAN Lakwijk-Vondrovicova E
- WAGENVOORT C A Management of primary pulmonary hypertension: correspondence 554
- *see also* Yamaki S & Wagenvoort C A
- WAINWRIGHT R J *see* Davies D W *et al*
- WALESBY R K *see* Kay P H *et al*
- WALKER J *see* Cheesman M G *et al*
- WALKER L *see* Timmis A D *et al*
- WALKER P R *see* Papouchado M *et al*
- WALTON S (& Costa D C, Ell P J, Emanuel R W) Myocardial imaging with iodine-123 meta-iodobenzylguanidine 617 P
- WANN L S *see* Daley P J *et al*
- WARNES C *see* Somerville J & Warnes C
- WARNES C A (& Somerville J) The fate of adults with tricuspid atresia and normally related great arteries 640 P
- WEBB-PEPLOE M M *see* Dawson J R *et al*
- Joy M *et al*
- WEIL J (& Lang R E, Brangenberg R, Sebening W, Dohlemann C, Bühlmeier K) Atrial distension may be a stimulus for the release of atrial natriuretic peptide in children with cardiac diseases 624 P
- WEISSBERG P L *see* Smith S A *et al*
- WESTABY S *see* Ribeiro P *et al*
- WESTGATE C *see* Crake T *et al*
- Shapiro L M *et al*
- WHEATLEY D J *see* Simpson I A *et al*
- WHITFIELD A G W Bicentenary of *An Account of the Foxglove* 253
- WIESHAMMER S (& Delagardelle C, Sigel H A, Henze E, Adam W E, Stauch M) Radionuclide ventriculography in coronary artery disease: correspondence reply 658
- WILLIAMS B C *see* Shaw T R D *et al*
- WILLIAMS D G (& Olsen E G J) Prevalence of overt dilated cardiomyopathy in two regions of England 153
- WILLIAMS E D *see* Gibson C J *et al*
- WILSON A G *see* Dawkins K D *et al*
- WILSON N *see* Goldberg S J *et al*
- WILSON P A POOLE- *see* Poole-Wilson P A
- WILSON J *see* Cleland J *et al*
- WINKLER C *see* Reake S N *et al*
- WITCHITZ S *see* Veyrat C *et al*
- WLADIMIROFF J W *see* Stewart P A *et al*
- WOOD D *see* Savill J *et al*
- WRAIGHT E P *see* Ormerod O J M *et al*
- Stone D L *et al*
- Taylor N C *et al*
- WREN C (& Campbell R W F, Hunter S) Role of echocardiography in differential diagnosis of broad complex tachycardia 166
- WRIGHT B Y *see* Sanderson J B *et al*
- WRIGHT C *see* Levy R D *et al*
- Quyyumi A A *et al*
- WRIGHT C A *see* Quyyumi A A *et al*
- WRIGHT C M *see* Quyyumi A A *et al*
- WRIGHT J E C *see* Kay P H *et al*
- WYSE R K H *see* Ortiz E *et al*
- Robinson P J *et al*
- YACOB M *see* Quyyumi A A *et al*
- YACOB M H *see* Gibbs J L *et al*
- Mitchell A G & Yacoub M H
- Yusuf S *et al*
- YAMAKI S (& Wagenvoort C A) Comparison of primary plexogenic arteriopathy in adults and children. A morphometric study in 40 patients 428
- YUSHAK M *see* Packer M *et al*
- YUSUF S (& Mitchell A, Yacoub M H) Interrelation between donor and recipient heart rates during exercise after heterotopic cardiac transplantation 173
- ZABAG M AL *see* Al Zabag M
- ZERBE F (& Ponizyński A, Dyszkiewicz W, Ziemiański A, Dziągiewski T, Krug H) Functionless retained pacing leads in the cardiovascular system. A complication of pacemaker treatment 76
- ZEZULKA A *see* Petri M P *et al*
- ZHANG Y (& Ihlen H, Myhre E, Levorstad K, Nitter-Hauge S) Measurement of mitral regurgitation by Doppler echocardiography 384
- ZIEMIAŃSKI A *see* Zerbe F *et al*
- ZWAAN C DE *see* Zwaan C

SUBJECT INDEX

1985, Volume 54

- Ablation with low energies, AV nodal conduction (Boyd *et al.*). 651 P
- Absent pulmonary valve syndrome, surgical treatment (de Leval *et al.*). 629 P
- Ambulatory monitoring, characteristics of episodes of ST elevation or ST depression during (von Arnim *et al.*). 484
- Ambulatory pulmonary artery pressure monitoring, in angina pectoris evaluation (Levy *et al.*). 643 P
- Ambulatory pulmonary artery pressure monitoring, and significance of painless ST segment depression (Levy *et al.*). 623 P
- Amlodarone, effect on arrhythmia and left ventricular function in heart failure (Cleland *et al.*). 647 P
- Amlodarone, effect on pulmonary function (Higginson *et al.*). 612 P for improved survival in hypertrophic cardiomyopathy and ventricular tachycardia: correspondence (Crick: McKenna). 550 and sotalol, in ischaemic myocardium, contrasting effects (Cobbe & Manley). 645 P
- Aneurysm, left ventricular, the Wessex experience (Keenan *et al.*). 269
- Angina pectoris
acute, functional effects of regional left ventricular asynchrony during (Dawson & Gibson). 621 P
ambulatory pulmonary artery pressure monitoring evaluation (Levy *et al.*). 643 P
complicated by arrhythmias, effect of percutaneous transluminal coronary angioplasty (Molajo *et al.*). 375
exertional and rest, effects of beta blocker, calcium antagonist, and nitrate (Quyyumi *et al.*). 643 P
importance of chest pain in determining degree of ischaemia (Quyyumi *et al.*). 22
and myocardial revascularisation (Quyyumi *et al.*). 557
with normal coronary arteries, effects of vasodilators on exercise capacity and myocardial oxygen supply (Bugiardini *et al.*). 610 P
post-myocardial infarction, natural history (Daly *et al.*). 610 P
refractory variant, management with benzhexol hydrochloride (trihexyphenidyl hydrochloride): case report (Joy *et al.*). 448
reoperation after previous aorto-coronary bypass surgery; correspondence (Freeman & Nixon: Pidgeon). 552
unstable, effects of early PTCA on clinical course (Timmis *et al.*). 627 P
and sudden ischaemic death, intramyocardial platelet emboli (Davies & Thomas). 636 P
- Angiocardiography and cross sectional echocardiography, correlation in criss cross hearts (Robinson *et al.*). 61
- Angiography, coronary, reverse delta wave as reliable sign of impending ventricular fibrillation (Crick). 645 P
- Angioplasty
balloon, in congenital heart disease (Muller). 285
percutaneous transluminal coronary *see* Percutaneous transluminal coronary angioplasty
- Angiotensin converting enzyme inhibitors, in heart failure (Dollery & Corr). 234
- Aorta, Aortic
arch interrupted, management (Bunton *et al.*). 625 P
persistent left sided fifth, neonate: case report (Cabrera *et al.*). 105
ascending Doppler measurement during exercise (Daley *et al.*). 562
compliance, mitral valve prolapse, and skin collagen, in joint hypermobility syndrome (Handler *et al.*). 501
left ventricular tunnel, management: case report (Ribeiro *et al.*). 333
regurgitation, assessment of ventricular function by phase analysis of equilibrium radionuclide ventriculography (Ormerod *et al.*). 638 P
captopril mediated decrease (Reske *et al.*). 415
stenosis, in adults, measured by Doppler echocardiography (Hengrenas & Hatle). 396
beneficial effect of beta blockade (Stockms *et al.*). 655 P
valvar, and hypertrophic cardiomyopathy, comparison of ejection dynamics (Stockms *et al.*). 621 P
- Aortic valve replacement, post-pericardiotomy syndrome and coronary occlusion after, association between: case report (de Scheerder *et al.*). 445
prolapse, prevalence and clinical significance (Shapiro *et al.*). 179
- Aortitis, diffuse non-specific, with multiple saccular aneurysms and aorto-enteric fistula: case report (Mukhopadhyay *et al.*). 102
- Aortocoronary bypass surgery, reoperation for angina: correspondence (Freeman & Nixon: Pidgeon). 552
see also Coronary artery bypass
- Aortography, descending, with balloon inflation (Rao). 527
- Apolipoprotein B values, skin, in normocholesterolaemic patients with coronary artery disease, a discriminatory test: correspondence (Doust-Blazy *et al.*). 452
- Arrhythmias
atrial, after cardiopulmonary bypass, sotalol in (Campbell *et al.*). 86
complicating angina, effect of percutaneous transluminal coronary angioplasty (Molajo *et al.*). 375
in hypertrophic cardiomyopathy, children and adolescents, incidence and relation to prognosis (McKenna *et al.*). 632 P
and left ventricular function, in heart failure, effect of amlodarone (Cleland *et al.*). 647 P
and left ventricular hypertrophy in essential hypertension (McLenahan *et al.*). 645 P
ventricular, spontaneous variability and effect on optimal duration of electrocardiographic monitoring required (Mulrow *et al.*). 644 P
- Artefactual ST segment abnormalities, due to electrocardiograph design (Tayler & Vincent). 121
- Arteriograms, coronary, routine diagnostic, for regional myocardial shortening assessment (Perry & Shiu). 620 P
- Aspirin treatment, and prostacyclin production in saphenous vein (Angelini *et al.*). 636 P
- Atenolol, effect on physiological response to exercise (Gordon *et al.*). 96
- Atheromatous wall, ultraviolet laser wavelengths selected for (Barker *et al.*). 635 P
- Atrial
distension, stimulus for release of atrial natriuretic peptide, in children with cardiac diseases (Well *et al.*). 624 P
fibrillation, and chronic nicotine ingestion: case report (Stewart & Catterall). 222
induced by implanted automatic defibrillator: case report (Jordans *et al.*). 605
in Wolff-Parkinson-White syndrome, effect of exercise on ventricular response (Crick *et al.*). 80
septal defect, functional and anatomical correlates, echocardiography (Forfar & Godman). 193
preoperative and post-operative pulmonary function tests, relation to pulmonary artery pressure and pulmonary: systemic flow ratio (Schofield *et al.*). 577
shunting and valvar regurgitation, magnetic resonance quantification (Underwood *et al.*). 616 P
spleen, right, presenting as atrial tumour: case report (Kuyjer *et al.*). 337
stimulation, sinus node sequences after, similarities of effects of different methods (Hedde *et al.*). 568

Atrioventricular

- conduction, transvenous fulguration of, exercise capacity and heart rhythm following (Schofield *et al.*). 614 P
- re-entry tachycardia, adaptation of overdrive pacing rate for termination with change in posture, relevance for automatic software pacemakers (Rowland *et al.*). 642 P
- and sinoatrial block, in thyrotoxic crisis. case report (Kramer *et al.*). 600

Balloon

- inflation, and descending aortography (Rao). 527
- valvuloplasty and angioplasty, in congenital heart disease (Miller). 285
- valvuloplasty, percutaneous, for pulmonary valve stenosis, infants and children (Sullivan *et al.*). 435

Behçet's disease, valve prolapse (Lu-Li *et al.*). 100Benzhexol hydrochloride (trihexyphenidyl hydrochloride), in management of refractory variant angina: case report (Joy *et al.*). 448

Beta blockade

- in aortic stenosis, beneficial effect (Stockins *et al.*). 655 P
- compared with flecainide, in ventricular response during exercise in established atrial fibrillation in digitalised patients (Agarwal *et al.*). 611 P
- effect on potassium homeostasis following myocardial infarction (Petri *et al.*). 646 P
- calcium antagonist, and nitrate, in exertional and rest angina (Quyyumi *et al.*). 643 P

Bleeding complications of intracoronary fibrinolytic therapy, in myocardial infarction, assessment of risk in a randomised trial (Verheugt *et al.*). 455

Blood

- coronary, transit, effects of nifedipine assessed by parametric digital subtraction angiography (Hayward *et al.*). 650 P
- pressure, linoleic acid, leucocyte sodium transport, and free calcium (Heagerty *et al.*). 635 P

Breathlessness, in chronic heart failure, origins (Lipkin & Poole-Wilson). 609 P

Budgeting, clinical, in cardiology and cardiac surgery (Parker *et al.*). 631 PCalcitonin gene related peptide, and coronary vasodilatation (McEwan *et al.*). 643 P

Calcium

- antagonist, beta blocker, and nitrate, in exertional and rest angina (Quyyumi *et al.*). 643 P
- blockade, attenuation of abnormal response to cold pressor stimulation in ischaemia and normal coronary arteries (Dymond *et al.*). 637 P
- free, linoleic acid, leucocyte sodium transport, and blood pressure (Heagerty *et al.*). 635 P
- role in induction of cardiac hypertrophy and myofibrillar disarray (Pearce *et al.*). 420

Captopril

- adding, or increasing diuretics, in moderate cardiac failure (Cowley *et al.*). 638 P
- concentrations, plasma free, during short and long term treatment with oral captopril for heart failure (Shaw *et al.*). 160
- mediated decrease of aortic regurgitation (Reake *et al.*). 415

Cardiac

failure *see* Heart failure

- hypertrophy, hypertrophic cardiomyopathy, and hyperparathyroidism, an association (Symons *et al.*). 539
- infarction, treated with intravenous streptokinase, follow up to two years in 108 patients (O'Keefe *et al.*). 619 P
- mortality, and changing digoxin potency, England and Wales 1968-76 (Tunstall-Pedoe). 243
- rejection from intramyocardial markers, functional correlates (Amende *et al.*). 653 P
- surgery, prostacyclin therapy during (Fessatidis *et al.*). 629 P
- subpulmonary pleural effusions after, children (O'Callaghan

et al.). 593

transplantation: correspondence (Hess). 555

heterotopic, interrelation between donor and recipient heart rates during exercise after (Yusuf *et al.*). 173

orthotopic, conduction between donor and recipient atria following (Mitchell & Yacoub). 615 P

tumour, with characteristics of splenic tissue: case report (Kuijjer *et al.*). 337

Cardiomyopathy, familial right ventricular dilated (Ibsen *et al.*). 156

overt dilated, prevalence in two regions of England (Williams & Olsen). 153

see also Hypertrophic cardiomyopathy

Cardiopulmonary bypass

atrial arrhythmias after, sotalol in (Campbell *et al.*). 86

hypertension after, factors relating to development (Cooper *et al.*). 91

Cardiovascular fitness, improving coronary risk profile (Findlay *et al.*). 656 P

Cardioversion, temporary transvenous, for recurrent ventricular tachyarrhythmias (Lewis *et al.*). 612 P

Cataract, congenital, hypertrophic cardiomyopathy associated with mitochondrial myopathy of voluntary muscles (Sengers *et al.*). 543

Catheterisation, cardiac, data, and Doppler estimates of aortic flow velocities, pitfalls in comparison (Carreras *et al.*). 649 P

Cerebral consequences of coronary artery surgery (Smith *et al.*). 630 P

Chest pain, importance in determining degree of ischaemia in angina pectoris (Quyyumi *et al.*). 22

Chylopericardium, rare complication of a Waterston shunt: case report (Hamilton *et al.*). 548

Cold pressor stimulation, attenuation by calcium blockade of abnormal response in ischaemia and normal coronary arteries (Dymond *et al.*). 637 P

Collagen, skin, mitral valve prolapse, and aortic compliance, in joint hypermobility syndrome (Handler *et al.*). 501

Computed tomography, urine, to estimate coronary artery bypass graft patency (Rees *et al.*). 655 P

Conduction between donor and recipient atria, following orthotopic cardiac transplantation (Mitchell & Yacoub). 615 P

Congenital heart disease

children, prostacyclin in enhancement of selective pulmonary vasodilator effect of oxygen (Bush *et al.*). 625 P

different types, lung biopsies, computed-assisted structural and functional correlations (Hayworth). 625 P

embolisation procedures (Reidy *et al.*). 184

familial recurrence (Allen *et al.*). 613 P

spectrum detected echocardiographically in prenatal life (Allan *et al.*). 523

first year of life, necropsy study (Hegerty *et al.*). 583

Coronary

artery bypass surgery, graft assessment, digital subtraction angiography, clinical applicability (Hayward & Hunter). 357

patency estimation, by cine computed tomography, sensitivity and specificity (Rees *et al.*). 655 P

and hyperlipidaemia: correspondence (Singh & Sosa; Thompson & Sapsford). 453

to right coronary artery, with and without endarterectomy, patency at one year (Kay *et al.*). 489

left ventricular aneurysmectomy and improvement of ventricular function (Taylor *et al.*). 145

neurological complications (Shaw *et al.*). P

see also Aortocoronary bypass

new septal wall motion abnormalities, role of transient ischaemia and perioperative myocardial infarction (Ribeiro *et al.*). 140

reoperation for angina: correspondence (Freeman & Nixon; Pidgeon). 552

right, with and without endarterectomy, patency at one year (Kay *et al.*). 489

- artery disease, detection, exercise technetium ventriculography and exercise thallium imaging compared (McGhie *et al.*) 617 P
- lipoprotein profiles in veteran endurance athletes and age matched subjects (Northcote *et al.*) 647 P
- prevention and screening, strategies: editorial (Oliver). 1
- and radionuclide ventriculography: correspondence (Underwood: Wieshammer *et al.*) 658
- skin apolipoprotein B values in normocholesterolaemic patients, a discriminatory test: correspondence (Doust-Blazy *et al.*) 452
- three vessel, coronary anatomy in various manifestations of (Quyyumi *et al.*) 362
- ectasia, prevalence and clinical significance in 4993 patients (Hartnell *et al.*) 392
- left, anomalous origin, from pulmonary artery, adult: case report (Vesterlund *et al.*) 110
- anomalous origin from pulmonary artery: ligation versus establishment of two coronary systems (Burton *et al.*) 624 P
- main stem, stenosis (Cheecaman *et al.*) 631 P
- normal, and ischaemia, attenuation by calcium blockade of abnormal response to cold pressor stimulation (Dymond *et al.*) 637 P
- occlusion, acute, during percutaneous transluminal coronary angioplasty (Shru *et al.*) 129
- and post-pericardiotomy syndromes, after aortic replacement, association between: case report (de Scheerder *et al.*) 445
- perforation, benign, during percutaneous transluminal coronary angioplasty (Meier). 33
- surgery, cerebral consequences (Smith *et al.*) 630 P
- trials, practical implications: review (Julian). 343
- thrombus, risk factor for acute vessel occlusion during percutaneous transluminal coronary angioplasty, improving results (Sugrue *et al.*) 627 P
- blood transit, effects of nifedipine assessed by parametric digital subtraction angiography (Hayward *et al.*) 650 P
- ostial stenosis, isolated, a previously unrecognised clinical syndrome (Miller *et al.*) 611 P
- sinus, left of Valsalva *see* Valsalva, left coronary sinus
- stenoses, multiple, and percutaneous transluminal coronary angioplasty (Ilsley & Ablett). 627 P
- vasodilatation by calcitonin gene related peptide (McEwan *et al.*) 643 P
- Corrections 114
- Correspondence
- Cardiac transplantation (Hess). 555
- Coronary artery bypass grafting and hyperlipidaemia (Singh & Sosa: Thompson & Sapsford). 453
- Improved survival with amiodarone in patients with hypertrophic cardiomyopathy and ventricular tachycardia (Crick: McKenna). 550
- Lead specificity of the maximum ST/heart rate/slope response (Layton). 554
- Left ventricular gradients in hypertrophic cardiomyopathy (Pollock: McKenna & Sugrue). 113
- Management of primary pulmonary hypertension (Wagenvoort: Oakley). 554
- Pathways of preferential arterial conduction (Anderson & Becker). 226
- Radionuclide ventriculography in coronary artery disease (Underwood: Wieshammer *et al.*) 658
- Reoperation for angina after previous aortocoronary bypass surgery (Freeman & Nixon: Pidgeon). 552
- Skin apolipoprotein B values in normocholesterolaemic patients with coronary artery disease: a discriminatory test? (Doust-Blazy *et al.*) 452
- Cross cross hearts, cross sectional echocardiography and angiocardiology, correlation (Robinson *et al.*) 61
- Cross sectional echocardiography
- and angiocardiology, correlation in cross cross hearts (Robinson *et al.*) 61
- and colour Doppler, superimposed, simultaneous display, and localisation of ventricular septal defects (Ortiz *et al.*) 53
- segmental wall motion analysis, reproducibility and sources of variability (Peart *et al.*) 617 P
- DDD pacemakers and myopotential sensing (Sanderson *et al.*) 651 P
- Death, sudden cardiac
- ischaemic heart disease and prodromes (Madsen). 27
- and unstable angina, intramyocardial platelet emboli (Davies & Thomas). 636 P
- postmortem coronary arteriography following (Dawkins *et al.*) 611 P
- Defibrillator, automatic, implanted, inducing atrial fibrillation, efficacy: case report (Jordaens *et al.*) 605
- Diabetes
- and impairment of left ventricular function, evidence for specific heart muscle disease (Fisher *et al.*) 656 P
- myocardial infarct size and mortality (Gwilt *et al.*) 466
- Digital subtraction angiography in coronary artery bypass graft assessment, clinical applicability (Hayward & Hunter). 357
- Digitalis
- bicentennial celebrations of *Withering, William: An account of the Foxglove* 251
- and cardiac glycosides (Hollman). 258
- Digitalis lanata*, cultivation and breeding, Netherlands (Mast-enbroek). 262
- where are we now: editorial (Chamberlain). 227
- Withering and the foxglove: the making of a myth (Krikler). 256
- Digoxin
- in heart failure (Dollery & Corr). 234
- potency, changes, and cardiac mortality, England and Wales 1968-76 (Tunstall-Pedoe). 243
- rapid plasma, assay, in outpatients, useful routine technique (Savill *et al.*) 248
- Disopyramide and flecainide compared, in suppressing chronic ventricular premature complexes (Trosser *et al.*) 644 P
- Diuretic(s)
- induced hypokalaemia, arrhythmogenic potential, in mild hypertension and ischaemic heart disease (Stewart *et al.*) 290
- increasing, or adding captopril, in moderate cardiac failure, comparison (Cowley *et al.*) 638 P
- resistant cardiac failure, fluid removal by haemofiltration: case report (Morgan *et al.*) 218
- Dopexamine, acute haemodynamic and metabolic effects of new dopaminergic receptor agonist, in chronic heart failure (Dawson *et al.*) 313
- Doppler echocardiography
- colour, and cross sectional echocardiographic images, superimposed, simultaneous display, and localisation of ventricular septal defects (Ortiz *et al.*) 53
- evaluation of aortic flow velocities and cardiac catheterisation data, pitfalls in comparison (Carreras *et al.*) 649 P
- of discrete subvalvar and multilevel outflow tract obstruction, congenital heart disease (Sutherland *et al.*) 626 P
- of elliptical area technique for calculating mitral blood flow (Goldberg *et al.*) 68
- investigational bioprosthesis valve replacement, 155 patients (Simpson *et al.*) 631 P
- of pressure gradient in infundibular pulmonary stenosis (Houston *et al.*) 618 P
- surgical shunt patency (Mulholland & Shields). 639 P
- following anatomical correction of transposition of great arteries (Gibbs *et al.*) 652 P
- investigations, two dimensional and pulsed, in early systolic murmurs, children (Jordan). 618 P
- measurement in ascending aorta during exercise (Daley *et al.*) 562

- measuring aortic stenosis in adults (Hegrenae & Hatle). 396
 measuring changes in left ventricular stroke volume (Ihlen *et al.*). 378
 measuring mitral regurgitation (Zhang *et al.*). 384
 for non-invasive haemodynamic assessment of mitral prosthetic function (Simpson *et al.*). 648 P
 technique, in localisation and evaluation of valvar prosthetic dysfunction (Veyrat *et al.*). 273
 two methods, pulmonary hypertension assessment (Thwaites *et al.*). 650 P
- Double outlet right ventricle
 early prenatal detection by echocardiography: case report (Stewart *et al.*). 340
 and transposition of great arteries, anatomic correction, early and intermediate structural and functional considerations (Lincoln *et al.*). 639 P
- Drug treatment, heart failure (Dollery & Corr). 234
- Ebstein's anomaly, diagnosis and natural history (Radford *et al.*). 517
- Echocardiography
 changing features of hydatid cyst of heart: case report (Kostucki *et al.*). 224
 to detect spectrum of congenital heart disease in prenatal life (Allen *et al.*). 523
 for early prenatal detection of double outlet right ventricle: case report (Stewart *et al.*). 340
 functional and anatomical correlates in atrial septal defect (Forfar & Godman). 193
 role in differential diagnosis of broad complex tachycardia (Wren *et al.*). 166
 sensitivity in infective endocarditis (Nihoyannopoulos *et al.*). 648 P
 in tuberculous sclerosis (Gibbs). 653 P
- Editorials
 Digitalis: where are we now? (Chamberlain). 227
 Do we need a new standard for electrocardiography? (Gold). 119
 Strategies for preventing and screening for coronary heart disease (Oliver). 1
 The challenge and the reproach of infective endocarditis (Goodwin). 115
- Eisenmenger's syndrome, and heart-lung transplantation (McGregor *et al.*). 630 P
- Ejection dynamics, in hypertrophic cardiomyopathy and valvar aortic stenosis compared (Stockins *et al.*). 621 P
- Electrocardiograph, Mason-Likar "modified" exercise, essentially identical to 12 standard leads (Papouchado *et al.*). 523 P
- Electrocardiography
 new standard: editorial (Gold). 119
 ambulatory, in tuberculous sclerosis (Gibbs). 653 P
- Emboli, platelet, intramyocardial, in unstable angina and sudden ischaemic death (Davies & Thomas). 636 P
- Embolisation procedures, in congenital heart disease (Reidy *et al.*). 184
- Emphysema, surgical, causing permanent pacemaker failure: case report (Smith *et al.*). 220
- Enalapril
 in congestive cardiac failure, controlled trial (McGrath *et al.*). 405
 effects in heart failure (Cleland *et al.*). 305
 effects on renal function in heart failure (Cleland *et al.*). 655 P
- Endocarditis, infective (bacterial) *see* Infective endocarditis
- Epoprostenol *see* Prostacyclin
- Exercise
 ascending aorta during, Doppler measurement (Daley *et al.*). 562
 electrophysiology in Wolff-Parkinson-White syndrome (Crick *et al.*). 80
 physiological response, effect of atenolol (Gordon *et al.*). 96
 radionuclide ventriculography, children, normal values for exercise variables and right and left ventricular function (Parrish *et al.*). 509
 testing, six weeks and 18 months after myocardial infarction, patients under 55 years (Pearl *et al.*). 622 P
 ten days and three months after myocardial infarction compared, relation to pattern of coronary disease (Pumphrey *et al.*). 623 P
 transient Q waves followed by left anterior fascicular block during: case report (Rebuzzi *et al.*). 107
 ventriculography and exercise thallium imaging compared (McGhie *et al.*). 617 P
see also other methods of testing and indications
- Fibrillation
 atrial, in Wolff-Parkinson-White syndrome, effect of exercise on ventricular response (Crick *et al.*). 80
 ventricular, in right coronary angiography, reverse delta wave as reliable sign (Crick). 645 P
- Fibrinolytic therapy, intracoronary, in myocardial infarction, bleeding complications (Verheugt *et al.*). 455
- Flecainide
 compared with beta blockade, in ventricular response during exercise in established atrial fibrillation in digitalised patients (Agarwal *et al.*). 611 P
 and disopyramide compared, in suppressing chronic ventricular premature complexes (Trosser *et al.*). 644 P
- Four dimensional cardiac imaging (Smith & Quarendon). 616 P
- Forxglove *see* Digitalis
- Glycosides, cardiac
 in exertion of positive inotropism in sinus rhythm (Tan *et al.*). 654 P
 and plants (Hollman). 258
- Gold-195m, in quantification of intracardiac shunts, new radionuclide with short half life (Stone *et al.*). 495
- Haemofiltration, for fluid removal in diuretic resistant cardiac failure: case report (Morgan *et al.*). 218
- Heart failure
 acute haemodynamic and metabolic effects of doxamine, new dopaminergic receptor agonist (Dawson *et al.*). 313
 chronic ischaemic, factors influencing survival and mode of death (Glover & Littler). 613 P
 congestive, controlled trial of enalapril (McGrath *et al.*). 405
 diuretic resistant, fluid removal by haemofiltration: case report (Morgan *et al.*). 218
 drug treatment (Dollery & Corr). 234
 effect of amiodarone on arrhythmia and left ventricular function (Cleland *et al.*). 647 P
 effects of enalapril (Cleland *et al.*). 305; 655 P
 milrinone in: part I. Acute effects on left ventricular systolic function and myocardial metabolism (Timmis *et al.*). 36, part II. Effects on exercise haemodynamics during short term treatment (Timmis *et al.*). 42
 moderate, increasing diuretics or adding captopril, comparison (Cowley *et al.*). 638 P
 origins of breathlessness (Lipkin & Poole-Wilson). 609 P
 plasma free captopril concentrations during short and long term treatment with oral captopril (Shaw *et al.*). 160
 severe, maximal force, fibre type, and enzymatic activity in quadriceps, mechanism for reduced exercise capacity (Lipkin *et al.*). 622 P
- Heart-lung transplantation, for Eisenmenger's syndrome (McGregor *et al.*). 630 P
- Heart muscle disease, specific, and impairment of left ventricular function in diabetes (Fisher *et al.*). 656 P
- Heart rates, donor and recipient, during exercise after heterotopic cardiac transplantation (Yusuf *et al.*). 173
- Hydatid cyst of heart, changing echocardiographic features: case report (Kostucki *et al.*). 224
- Hypercalcaemia
 idiopathic infantile, and associated cardiac anomalies, clinical and echocardiographic study (Balaram *et al.*). 652 P

- cardioplegic sodium and damage to vascular endothelium, studies on vascular responsiveness, rat heart (Saldanha *et al.*). 654 P
- intracoronary, localised, risk of laser angioplasty (Bowker *et al.*). 637 P
- Hyperlipidaemia, and coronary artery bypass grafting: correspondence (Singh & Sosa; Thompson & Sapsford). 453
- Hyperparathyroidism, cardiac hypertrophy, and hypertrophic cardiomyopathy, an association (Symons *et al.*). 539
- Hypertension
after cardiopulmonary bypass, factors relating (Cooper *et al.*). 91
- essential, and arrhythmias and left ventricular hypertrophy. (McLenachan *et al.*). 645 P
- mild, inappropriate left ventricular hypertrophy in, echocardiographic study, middle aged subjects (Crake *et al.*). 649 P
- and ischaemic heart disease, arrhythmogenic potential of diuretic induced hypokalaemia (Stewart *et al.*). 290
- prevalence in habitually salted-tea drinkers, Northern Kashmir (Mir *et al.*). 613 P
- pulmonary, assessment by two Doppler echocardiographic methods (Thwaites *et al.*). 650 P
- Hypertrophic cardiomyopathy
arrhythmia in children and adolescents, incidence and relation to prognosis (McKenna *et al.*). 632 P
- cardiac hypertrophy, and hyperparathyroidism, an association (Symons *et al.*). 539
- haemodynamic and symptomatic improvements using dual chamber pacing (Erwin *et al.*). 641 P
- left ventricular gradients correspondence (Pollick; McKenna & Sugrue). 113
- and mitochondrial myopathy of voluntary muscles, and congenital cataract (Sengers *et al.*). 543
- and myofibrillar disarray, role of calcium (Pearce *et al.*). 420
- nuclear magnetic resonance in (Been *et al.*). 48
- simulating an infiltrative myocardial disease: case report (Frustaci *et al.*). 329
- and valvar aortic stenosis, comparison of ejection dynamics (Stockins *et al.*). 621 P
- and ventricular tachycardia, improved survival with amiodarone correspondence (Crick; McKenna). 550
- Hypokalaemia, diuretic induced, arrhythmogenic potential, in mild hypertension and ischaemic heart disease (Stewart *et al.*). 290
- Hypoplastic left heart syndrome and 45X karyotype (van Egmond *et al.*). 653 P
- Hypothermic circulatory arrest, elective, as cause of brain damage (Ekroth *et al.*). 640 P
- Hypothyroidism, and asymmetric septal hypertrophy, children (Altman *et al.*). 533
- Imaging, cardiac
four dimensional (Smith & Quarendon). 616 P
- myocardial, with iodine-123 meta-iodobenzylguanidine (Walton *et al.*). 617 P
- Infarct
site, prognostic importance of exercise induced ST elevation post-infarction (Handler & Sowton). 646 P
- size, myocardial, and mortality, diabetic patients (Gwilt *et al.*). 466
- Infective endocarditis
challenge and reproach: editorial (Goodwin). 115
- current incidence and mortality (Skehan *et al.*). 614 P
- sensitivity of echocardiography (Nihoyannopoulos *et al.*). 648 P
- Infundibular pulmonary stenosis, Doppler estimation of pressure gradient in (Houston *et al.*). 618 P
- Inotropes, in heart failure (Dollery & Corr). 234
- Inotropism, positive, in sinus rhythm, cardiac glycosides in exertion of (Tan *et al.*). 654 P
- Intracoronary thrombolysis, coronary reocclusion during, effect of nitrates (Hackett *et al.*). 619 P
- Intramyocardial markers, functional correlates of cardiac rejection (Amende *et al.*). 653 P
- Iodine-123 meta-iodobenzylguanidine, for myocardial imaging (Walton *et al.*). 617 P
- Ischaemia
and sinus node disease (Linker *et al.*). 612 P
- transient role in genesis of new septal wall motion abnormalities after coronary bypass surgery (Ribeiro *et al.*). 140
- Ischaemic heart disease
and mild hypertension, arrhythmogenic potential of diuretic induced hypokalaemia (Stewart *et al.*). 290
- and prodromes of sudden cardiac death (Madsen). 27
- Ischaemic myocardium, contrasting effects of amiodarone and sotalol (Cobbe & manley). 645 P
- Joint hypermobility syndrome, mitral valve prolapse, aortic compliance, and skin collagen in (Handler *et al.*). 501
- Laser
angioplasty, coronary, in vivo, acute and chronic angiographic effects (Bowker *et al.*). 634 P
- localised intracoronary hyperkalaemia risk (Bowker *et al.*). 637 P
- argon, recanalisation of acutely thrombosed coronary arteries, live dogs (Fenech *et al.*). 628 P
- wavelengths selected for atheromatous as opposed to normal arterial wall (Bowker *et al.*). 635 P
- Lead specificity, maximum ST/heart rate slope response. correspondence (Layton). 554
- Left anterior fascicular block, following transient Q waves, during exercise: case report (Rebuzzi *et al.*). 107
- Leucocyte sodium transport, free calcium, linoleic acid, and blood pressure (Heagerty *et al.*). 635 P
- Linoleic acid, leucocyte sodium transport, free calcium, and blood pressure (Heagerty *et al.*). 635 P
- Lipoprotein profiles, in coronary artery disease, veteran endurance athletes, age matched subjects and controls (Northcote *et al.*). 647 P
- Lung biopsies, in different types of congenital heart disease, computer-assisted structural and functional correlations (Haworth). 625 P
- Main stem stenosis, safety (Cheesman *et al.*). 631 P
- Markers, intramyocardial, functional correlates of cardiac rejection (Amende *et al.*). 653 P
- Mason-Likar "modified" exercise electrocardiograph, essentially identical to 12 standard leads (Papouchado *et al.*). 623 P
- Meta-iodobenzylguanidine, iodine-123, for myocardial imaging (Walton *et al.*). 617 P
- Milrinone, in heart failure: part I. Acute effects on left ventricular systolic function and myocardial metabolism (Timmis *et al.*). 36, part II. Effects on haemodynamics during short term treatment (Timmis *et al.*). 42
- Mitral
blood flow, calculation by Doppler echocardiography, evaluation of elliptical area technique (Goldberg *et al.*). 68
- prosthetic function, non-invasive haemodynamic assessment by Doppler ultrasound (Simpson *et al.*). 648 P
- regurgitation, measurement by Doppler echocardiography (Zhang *et al.*). 384
- valve prolapse, aortic compliance, and skin collagen, in joint hypermobility syndrome (Handler *et al.*). 501
- Mustard procedure, and transposition of great arteries, adults and adolescents (Somerville & Warnes). 633 P
- Myocardial
infarct size and mortality, diabetic patients (Gwilt *et al.*). 466
- infarction, acute, early recanalisation, recommendation (Hugenholz). 636 P
- exercise testing, six weeks and 18 months after, patients under 55 years (Pearl *et al.*). 622 P
- at ten days and three months compared, relation to pattern of coronary disease (Pumphrey *et al.*). 623 P

- intracoronary fibrinolytic therapy, bleeding complications (Verheugt *et al.*) 455
- late potentials after, analysis of signal averaged surface electrocardiogram (Skehan *et al.*) 642 P
- left ventricular function four weeks after, effect of early treatment with propranolol (Brown *et al.*) 351
- non-Q-wave, classification according to electrocardiographic changes (Ogawa *et al.*) 473
- and percutaneous transluminal coronary angioplasty, results (Isley & Ablett) 620 P
- perioperative, role in genesis of new septal wall motion abnormalities after coronary bypass surgery (Ribeiro *et al.*) 140
- post-, exercise induced ST elevation, prognostic importance and relation to site of infarct (Handler & Sowton) 646 P
- potassium homeostasis following, effect of beta blockade (Petri *et al.*) 646 P
- prognostic significance of delayed potentials and inducible ventricular tachycardia (Dennis *et al.*) 609 P
- and reciprocal ST depression (Odumuyiwa *et al.*) 479
- smoking and timolol (Rønnevik *et al.*) 134
- suitability of thrombolysis (Murray *et al.*) 620 P
- surgical versus non-surgical management (Brower *et al.*) 460
- and thrombolysis, ECG using precordial mapping (von Esen *et al.*) 6
- metabolism, uniformity (Tweddel *et al.*) 648 P
- rupture, occurrence and risk factors (Dellborg *et al.*) 11
- shortening, regional, assessment using routine diagnostic coronary arteriograms (Perry & Shiu) 620 P
- Myofibrillar disarray and hypertrophic cardiomyopathy, role of calcium (Pearce *et al.*) 420
- Myopathy, mitochondrial, of voluntary muscles, hypertrophic cardiomyopathy, and congenital cataract (Sengers *et al.*) 543
- Myopotential sensing and DDD pacemakers (Sanderson *et al.*) 651 P
- Natriuretic peptide, atrial, atrial distension as stimulus for release, children with cardiac diseases (Weil *et al.*) 624 P
- Nicotine ingestion, chronic, and atrial fibrillation: case report (Stewart & Catterall) 222
- Nifedipine, effects in coronary blood transit, parametric digital subtraction angiography assessment (Hayward *et al.*) 650 P
- Nitrates
- beta blocker, and calcium antagonist, in exertional and rest angina (Quyyumi *et al.*) 643 P
 - effect on coronary re-occlusion during intracoronary thrombolysis (Hackett *et al.*) 619 P
- Non-Q-wave myocardial infarction, classification according to electrocardiographic changes (Ogawa *et al.*) 473
- Notices 114, 226, 342, 454, 556, 660
- Nuclear magnetic resonance
- assessment of left ventricular wall motion (Rees *et al.*) 650 P
 - in hypertrophic cardiomyopathy (Been *et al.*) 48
 - quantification of atrial shunting and valvar regurgitation (Underwood *et al.*) 616 P
- Pacemakers
- automatic software, relevance in adaptation of overdrive pacing rate for termination of AV re-entry tachycardia with change in posture (Rowland *et al.*) 642 P
 - DDD, and myopotential sensing (Sanderson *et al.*) 651 P
 - insertion and therapy in cardiothoracic centre, eleven years' experience (Greenbaum & Balcon) 615 P
 - multi-programmable, essential for pacing in children (Ladusans *et al.*) 632 P
 - permanent, failure due to surgical emphysema: case report (Smith *et al.*) 220
- Pacing
- dual chamber, in hypertrophic cardiomyopathy, haemodynamic and symptomatic improvements (Erwin *et al.*) 641 P
 - leads, functionless retained, cardiovascular system, complicating pacemaker treatment (Zerbe *et al.*) 76
- Parametric digital subtraction angiography, and assessment of effects of nifedipine on coronary blood transit (Hayward *et al.*) 650 P
- Percutaneous transluminal coronary angioplasty
- acute coronary occlusion during (Shiu *et al.*) 129
 - in acute myocardial infarction, results (Isley & Ablett) 620 P
 - benign coronary perforation during (Meier) 33
 - coronary artery thrombus as risk factor for acute vessel occlusion during, improving results (Sugrue *et al.*) 627 P
 - effect on arrhythmias complicating angina (Molajo *et al.*) 375
 - effects on clinical course of unstable angina (Timmis *et al.*) 627 P
 - emergency surgery following (Hamilton *et al.*) 634 P
 - prevention of regional myocardial ischaemia during, effects of infusing arterial blood (Timmis *et al.*) 628 P
 - results in multiple coronary stenoses (Isley & Ablett) 627
 - spontaneous recanalisation of side branches occluded during: case report (Shiu & Singh) 215
 - success and complication rates with and without previous myocardial infarction (Perry *et al.*) 634 P
 - timing for assessment by exercise testing (Polydorou *et al.*) 626 P
- Persistent ductus arteriosus, technique for evaluating size (Rao) 527
- Plants and cardiac glycosides (Hollman) 528
- Pleural effusions, subpulmonary, after cardiac surgery, children (O'Callaghan *et al.*) 593
- Plexogenic arteriopathy, primary, comparison in adults and children, 40 patients (Yamaki & Wagenvoort) 428
- Post-pericardiotomy syndrome and coronary occlusion after aortic valve replacement, association between: case report (de Scheerder *et al.*) 445
- Potassium homeostasis following myocardial infarction, effect of beta blockade (Petri *et al.*) 646 P
- Preferential arterial conduction, pathways: correspondence (Anderson & Becker) 226
- Prenatal
- detection, early of double outlet right ventricle by echocardiography: case report (Stewart *et al.*) 340
 - life, spectrum of congenital heart disease detected echocardiographically (Allan *et al.*) 523
- Propranolol, effect of early treatment on left ventricular function four weeks after myocardial infarction (Brown *et al.*) 351
- Prostacyclin
- production, in saphenous vein from patients receiving aspirin (Angelini *et al.*) 636 P
 - in enhancement of selective pulmonary vasodilator effect of oxygen in children with congenital heart disease (Bush *et al.*) 625 P
 - therapy during cardiac surgery (Fessatidis *et al.*) 629 P
- Pulmonary
- atrias, in prenatal life (Allan *et al.*) 640 P
 - staged repair, non-invasive assessment of pulmonary blood supply after (del Torso *et al.*) 209
 - blood supply, non-invasive assessment after staged repair of pulmonary atresia (del Torso *et al.*) 209
 - function tests, preoperative and postoperative, in atrial septal defect, relation to pulmonary artery pressure and pulmonary systemic flow ratio (Schofield *et al.*) 577
 - hypertension, assessment by two Doppler echocardiographic methods (Thwaites *et al.*) 650 P
 - primary, management: correspondence (Wagenvoort: Oakley) 554
 - valve stenosis, and percutaneous balloon valvuloplasty, infants and children (Sullivan *et al.*) 435
 - vascular resistance, assessment in ventricular septal defect (Neutze *et al.*) 633 P
- Q waves, transient, followed by left anterior fascicular block during exercise: case report (Rebuzzi *et al.*) 107
- Quadriceps, patients with severe heart failure, maximal force, fibre

- type, and enzymatic activity in, mechanism for reduced exercise capacity (Lipkin *et al.*). 622 *P*
- Radionuclide ventriculography
in coronary artery disease: correspondence (Underwood: Wieshammer *et al.*). 658
equilibrium, phase analysis, and assessment of ventricular function in aortic regurgitation (Ormerod *et al.*). 638 *P*
exercise, children, normal values for exercise variables and right and left ventricular function (Parrish *et al.*). 509
- Recanalisation
argon laser, acutely thrombosed coronary arteries, live dogs (Fenech *et al.*). 628 *P*
early, in acute myocardial infarction, recommendation (Hugenholz). 636 *P*
- Regurgitation
aortic, assessment of ventricular function by phase analysis of equilibrium radionuclide ventriculography (Ormerod *et al.*). 638 *P*
mitral, measurement by Doppler echocardiography (Zhang *et al.*). 384
"physiological" tricuspid and pulmonary, varying incidence (Upward *et al.*). 618 *P*
valvar, and atrial shunting, magnetic resonance quantification (Underwood *et al.*). 616 *P*
- Renal function in heart failure, effects of enalapril (Cleland *et al.*). 655 *P*
- Renin, plasma activity, in prediction of haemodynamic and clinical responses (Packer *et al.*). 298
- Re-occlusion, coronary, during intracoronary thrombolysis, effect of nitrates (Hackett *et al.*). 619 *P*
- Respiratory gas exchange, in assessment of impaired ventricular function (Lipkin *et al.*). 321
- Revascularisation, myocardial, in angina (Quyyumi *et al.*). 557
- Risk profile, coronary, cardiovascular fitness improving (Findlay *et al.*). 656 *P*
- Saccular aneurysm, rapid expansion on left coronary sinus of Valsalva, role for early surgical repair: case report (Faillace *et al.*). 442
- Salt intake, high, in tea, and prevalence of hypertension, Northern Kashmir (Mir *et al.*). 613 *P*
- Saphenous vein, from patients receiving aspirin, prostacyclin production (Angelini *et al.*). 636 *P*
- Screening, coronary heart disease, strategies: editorial (Oliver). 1
- Segmental wall motion analysis of cross sectional echocardiograms, reproducibility and sources of variability (Peart *et al.*). 617 *P*
- Septal
hypertrophy, asymmetric, and hypothyroidism, children (Altman *et al.*). 533
wall, new, motion abnormalities, after coronary bypass surgery, role of transient ischaemia and perioperative myocardial infarction (Ribeiro *et al.*). 140
- Shunts
intracardiac, quantification by gold-195m, new radionuclide with short half life (Stone *et al.*). 495
surgical, patency, assessment by Doppler (Mulholland & Shields). 639 *P*
- Sinoatrial and atrioventricular block, in thyrotoxic crisis: case report (Kramer *et al.*). 600
- Sinus node
disease, and ischaemia (Linker *et al.*). 612 *P*
sequences, after atrial stimulation, similarities of effects of different methods (Hedde *et al.*). 568
- Sinus rhythm, and cardiac glycosides in exertion of positive inotropism (Tan *et al.*). 654 *P*
- Smoking and timolol, after myocardial infarction (Rennevik *et al.*). 134
- Sotalol
and amiodarone, in ischaemic myocardium, contrasting effects (Cobbe & Manley). 645 *P*
in atrial arrhythmia, after cardiopulmonary bypass (Campbell *et al.*). 86
- ST segment
artefactual, abnormalities, due to electrocardiograph design (Tayler — Víncent). 121
depression, reciprocal, in myocardial infarction (Odemuyiwa *et al.*). 479
painless, significance assessed by ambulatory pulmonary artery pressure monitoring (Levy *et al.*). 623 *P*
elevation, exercise induced, post-infarction, prognostic importance and relation to site of infarct (Handler & Sowton). 646 *P*
or ST depression, characteristics of episodes during ambulatory monitoring (von Arnim *et al.*). 484
heart rate slope response, maximum, lead specificity: correspondence (Layton). 554
- Starr-Edwards
aortic valve replacement, isolated, long term evaluation (Hackett *et al.*). 629 *P*
isolated mitral valve replacement, models 6400 and 6120, ten year clinical evaluation (Fessatidis *et al.*). 638 *P*
- Streptokinase, intravenous, for severe early cardiac infarction, follow up to two years in 108 patients (O'Keefe *et al.*). 619 *P*
- Subpulmonary pleural effusions, after cardiac surgery, children (O'Callaghan *et al.*). 593
- Subvalvar, discrete, and multilevel outflow tract obstruction, congenital heart disease, Doppler evaluation (Sutherland *et al.*). 626 *P*
- Surgical versus non-surgical management, soon after myocardial infarction (Brower *et al.*). 460
- Tachyarrhythmias, ventricular, recurrent, temporary transvenous cardioversion for (Lewis *et al.*). 612 *P*
- Tachycardia
broad complex, role of echocardiography in differential diagnosis (Wren *et al.*). 166
ventricular, automatic diagnosis by new methods of electrogram analysis (Davies *et al.*). 641 *P*
improved survival with amiodarone: correspondence (Crick: McKenna). 550
- Thallium-201, to coronary arteries, new technique for showing relation of tomographic myocardial perfusion images (Gibson *et al.*). 367
- Thrombolysis
intracoronary, coronary reocclusion during, effect of nitrates (Hackett *et al.*). 619 *P*
and myocardial infarction, ECG using precordial mapping (von Essen *et al.*). 6
suitability in myocardial infarction (Murray *et al.*). 620 *P*
- Thyrotoxic crisis, atrioventricular and sinoatrial block: case report (Kramer *et al.*). 600
- Transplantation, cardiac see Cardiac transplantation
- Transplantation, heart-lung, for Eisenmenger's syndrome (McGregor *et al.*). 630 *P*
- Timolol and smoking, after myocardial infarction (Rennevik *et al.*). 134
- Transposition of great arteries
after Mustard procedure, adults and adolescents (Somerville & Warnes). 633 *P*
anatomical correction, Doppler echocardiography following (Gibbs *et al.*). 652 *P*
complete, with intact ventricular septum, left ventricular outflow tract obstruction, cross sectional echocardiography study (Robinson *et al.*). 201
and DORV, anatomic correction, early and intermediate structural and functional considerations (Lincoln *et al.*). 639 *P*
- Transvenous fulguration of atrioventricular conduction, exercise capacity and heart rhythm following (Schofield *et al.*). 614 *P*
- Tricuspid atresia and normally related great arteries, fate of adults (Warnes & Somerville). 640 *P*

- Tuberculoma, myocardial, with rupture and pseudoaneurysm formation, successful surgical treatment: case report (Halim *et al.*). 603
- Tuberous sclerosis
 echocardiography and ambulatory electrocardiography (Gibbs). 653 P
 and the heart, echocardiographic and electrocardiographic study (Gibbs). 596
- Two dimensional and pulsed Doppler investigations, early systolic murmurs, children (Jordan). 618 P
- Valsalva, left coronary sinus, and rapid expansion of a saccular aneurysm, role for early surgical repair: case report (Faillace *et al.*) 442
- Valves(s)
 prosthetic dysfunction, localisation and evaluation using Doppler technique (Veyrat *et al.*). 273
 regurgitation and atrial shunting, magnetic resonance quantification (Underwood *et al.*). 616 P
 prolapse, in Behçet's disease (Lu-Li *et al.*). 100
 replacement, bioprosthetic, degeneration, aortic versus mitral position compared (Ribeiro *et al.*). 630 P
 investigational, Doppler ultrasound assessment, 155 patients (Simpson *et al.*). 631 P
 mitral, isolated, Starr-Edwards models 6400 and 6120, ten year clinical evaluation (Fessatidis *et al.*). 638 P
- Valvuloplasty, balloon, in congenital heart disease (Miller). 285
- Vascular endothelium, damage, and hyperkalaemic cardioplegic solutions, studies on vascular responsiveness, rat heart (Saldanha *et al.*). 654 P
- Vasodilation therapy, in heart failure (Dollery & Corr). 234
- Ventricle, ventricular
 arrhythmia, spontaneous variability and effect on optimal duration of electrocardiographic monitoring required (Mulrow *et al.*). 644 P
 fibrillation, low energy endocardial countershock for treatment (Nathan *et al.*). 615 P
 in right coronary angiography, reverse delta wave as reliable sign (Crick). 645 P
 function, impaired, respiratory gas exchange in assessment (Lipkin *et al.*). 321
 left aneurysm, the Wessex experience (Keenan *et al.*). 269
 aneurysmectomy, and improvement of ventricular function in coronary bypass surgery (Taylor *et al.*). 145
 asynchrony, regional, during acute angina, functional effects (Dawson & Gibson). 621 P
 dysfunction, effect of xamoterol (Molajo & Bennett). 17
 function and arrhythmia, in heart failure, effect of amiodarone (Cleland *et al.*). 647 P
 four weeks after myocardial infarction, effect of early treatment with propranolol (Brown *et al.*). 351
 impairment in diabetics, evidence for specific heart muscle disease (Fisher *et al.*). 656 P
 gradients, in hypertrophic cardiomyopathy. correspondence (Pollick; McKenna & Sugrue) 113
 hypertrophy and arrhythmias in essential hypertension (McLenahan *et al.*). 645 P
 inappropriate, in mild hypertension, echocardiographic study, middle aged subjects (Crake *et al.*). 649 P
 outflow tract obstruction, in complete transposition of the great arteries with intact ventricular septum, cross sectional echocardiography study (Robinson *et al.*). 201
 stroke volume changes measured by Doppler echocardiography (Ihlen *et al.*). 378
 wall motion, magnetic resonance assessment (Rees *et al.*). 650 P
 premature complexes, chronic, suppression, flecainide and disopyramide compared (Trosser *et al.*). 644 P
 septal defect, assessment of pulmonary vascular resistance (Neutze *et al.*). 633 P
 localisation by simultaneous display of superimposed colour Doppler and cross sectional echocardiographic images (Ortiz *et al.*). 53
 supernormal period, clinical significance in man (Butrous *et al.*). 641 P
 tachyarrhythmias, recurrent, temporary transvenous cardioversion for (Lewis *et al.*). 612. P
 tachycardia, automatic diagnosis by new methods of electrogram analysis (Davis *et al.*). 641 P
 improved survival with amiodarone: correspondence (Crick; McKenna). 550
 low energy endocardial countershock for treatment (Nathan *et al.*). 615 P
- Waterston shunt, chylopericardium a rare complication: case report (Hamilton *et al.*). 548
- Withering, William
An account of the Foxglove, Historical address given at Edgbaston Parish Church, Birmingham (Whitfield). 253
 bicentennial celebrations 251
 and the foxglove: the making of a myth (Krikler). 256
- Williams-Beuren syndrome and associated cardiac anomalies, clinical and echocardiographic study (Balaram *et al.*). 652 P
- Wolff-Parkinson-White syndrome, effect of exercise on ventricular response to atrial fibrillation (Crick *et al.*). 80
- Xamoterol (ICI 118587), effect on left ventricular dysfunction (Molajo & Bennett). 17

BRITISH HEART JOURNAL

Volume 54
1985

BRITISH MEDICAL ASSOCIATION · TAVISTOCK SQUARE · LONDON WC1H 9JR

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CONTENTS OF VOLUME 54

Number 1

EDITORIAL: STRATEGIES FOR PREVENTING AND SCREENING FOR CORONARY HEART DISEASE	M F Oliver	1
MYOCARDIAL INFARCTION AND THROMBOLYSIS: ELECTROCARDIOGRAPHIC SHORT TERM AND LONG TERM RESULTS USING PRECORDIAL MAPPING	R von Essen, W Schmidt, R Uebis, B Edelmann, S Effert, J Silny, G Rau	6
RUPTURE OF THE MYOCARDIUM: OCCURRENCE AND RISK FACTORS	M Dellborg, P Held, K Swedberg, A Vedin	11
EFFECT OF XAMOTEROL (ICI 118587), A NEW BETA ₁ ADRENOCEPTOR PARTIAL AGONIST ON RESTING HAEMODYNAMIC VARIABLES AND EXERCISE TOLERANCE IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION	A O Molajo, D H Bennett	17
HOW IMPORTANT IS A HISTORY OF CHEST PAIN IN DETERMINING THE DEGREE OF ISCHAEMIA IN PATIENTS WITH ANGINA PECTORIS?	A A Quyyumi, C M Wright, L J Mockus, K M Fox	22
ISCHAEMIC HEART DISEASE AND PRODROMES OF SUDDEN CARDIAC DEATH: IS IT POSSIBLE TO IDENTIFY HIGH RISK GROUPS FOR SUDDEN CARDIAC DEATH?	J K Madsen	27
BENIGN CORONARY PERFORATION DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY	B Meier	33
MILRINONE IN HEART FAILURE: ACUTE EFFECTS ON LEFT VENTRICULAR SYSTOLIC FUNCTION AND MYOCARDIAL METABOLISM	A D Timmis, P Smyth, M Monaghan, L Walker, K Daly, A A McLeod, D E Jewitt	36
MILRINONE IN HEART FAILURE: EFFECTS ON EXERCISE HAEMODYNAMICS DURING SHORT TERM TREATMENT	A D Timmis, P Smyth, D E Jewitt	42
NUCLEAR MAGNETIC RESONANCE IN HYPERTROPHIC CARDIOMYOPATHY	M Been, D Kean, M A Smith, R H B Douglas, J J K Best, A L Muir	48
LOCALISATION OF VENTRICULAR SEPTAL DEFECTS BY SIMULTANEOUS DISPLAY OF SUPERIMPOSED COLOUR DOPPLER AND CROSS SECTIONAL ECHOCARDIOGRAPHIC IMAGES	E Ortiz, P J Robinson, J E Deanfield, R Franklin, F J Macartney, R K H Wyse	53
CROSS SECTIONAL ECHOCARDIOGRAPHIC AND ANGIOCARDIOGRAPHIC CORRELATION IN CRISS CROSS HEARTS	P J Robinson, V Kumpeng, F J Macartney	61
EVALUATION OF AN ELLIPTICAL AREA TECHNIQUE FOR CALCULATING MITRAL BLOOD FLOW BY DOPPLER ECHOCARDIOGRAPHY	S J Goldberg, D F Dickinson, N Wilson	68
FUNCTIONLESS RETAINED PACING LEADS IN THE CARDIOVASCULAR SYSTEM: A COMPLICATION OF PACEMAKER TREATMENT	F Zerbe, A Ponizyński, W Dyszkiewicz, A Ziemiański, T Dziegielewski, H Krug	76
EFFECT OF EXERCISE ON VENTRICULAR RESPONSE TO ATRIAL FIBRILLATION IN WOLFF-PARKINSON-WHITE SYNDROME	J C P Crick, D W Davies, P Holt, P V L Curry, E Sowton	80
INTRAVENOUS SOTALOL FOR THE TREATMENT OF ATRIAL FIBRILLATION AND FLUTTER AFTER CARDIOPULMONARY BYPASS: COMPARISON WITH DISOPYRAMIDE AND DIGOXIN IN A RANDOMISED TRIAL	T J Campbell, T P Gavaghan, J J Morgan	86
FACTORS RELATING TO THE DEVELOPMENT OF HYPERTENSION AFTER CARDIOPULMONARY BYPASS	T J Cooper, T H Clutton-Brock, S N Jones, J Tinker, T Treasure	91

EFFECT OF BETA ₁ SELECTIVE ADRENERGIC BLOCKADE ON PHYSIOLOGICAL RESPONSE TO EXERCISE N F Gordon, J P van Rensburg, H M S Russell, D L Kawalsky, C P Celliers, J F Cilliers, D P Myburgh	96
VALVE PROLAPSE IN BEHÇET'S DISEASE Shen Lu-Yi, Cui Guang-Gen, Liang Ru-Lian	100
CASE REPORTS	
DIFFUSE NON-SPECIFIC AORTITIS WITH MULTIPLE SACCULAR ANEURYSMS AND AORTO-ENTERIC FISTULA A K Mukhopadhyay, P Chopra	102
PERSISTENT LEFT SIDED FIFTH AORTIC ARCH IN A NEONATE A Cabrera, J Galdeano, I Lekuona	105
TRANSIENT Q WAVES FOLLOWED BY LEFT ANTERIOR FASCICULAR BLOCK DURING EXERCISE A G Rebuzzi, F Loperfido, L M Biasucci	107
ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY IN AN ADULT T Vesterlund, P E B Thomsen, O K Hansen	110
CORRESPONDENCE	113
NOTICES	114

Number 2

EDITORIAL: THE CHALLENGE AND THE REPROACH OF INFECTIVE ENDOCARDITIS J F Goodwin	115
EDITORIAL: DO WE NEED A NEW STANDARD FOR ELECTROCARDIOGRAPHS? R G Gold	119
ARTEFACTUAL ST SEGMENT ABNORMALITIES DUE TO ELECTROCARDIOGRAPH DESIGN D I Tayler, R Vincent	121
ACUTE CORONARY OCCLUSION DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY M F Shiu, N P Silverton, D Oakley, D Cumberland	129
EFFECT OF SMOKING HABITS AND TIMOLOL TREATMENT ON MORTALITY AND REINFARCTION IN PATIENTS SURVIVING ACUTE MYOCARDIAL INFARCTION P K Rønnevik, T Gundersen, A M Abrahamsen	134
ROLE OF TRANSIENT ISCHAEMIA AND PERIOPERATIVE MYOCARDIAL INFARCTION IN THE GENESIS OF NEW SEPTAL WALL MOTION ABNORMALITIES AFTER CORONARY BYPASS SURGERY P Ribeiro, P Nihoyannopoulos, S Farah, D W Moss, S Westaby, C M Oakley, R A Foale	140
DOES LEFT VENTRICULAR ANEURYSMECTOMY IMPROVE VENTRICULAR FUNCTION IN PATIENTS UNDERGOING CORONARY BYPASS SURGERY? N C Taylor, R Barber, P Crossland, E P Wraight, T A H English, M C Petch	145
PREVALENCE OF OVERT DILATED CARDIOMYOPATHY IN TWO REGIONS OF ENGLAND D G Williams, E G J Olsen	153
FAMILIAL RIGHT VENTRICULAR DILATED CARDIOMYOPATHY H H W Ibsen, U Baandrup, E E Simonsen	156
PLASMA FREE CAPTOPRIL CONCENTRATIONS DURING SHORT AND LONG TERM TREATMENT WITH ORAL CAPTOPRIL FOR HEART FAILURE T R D Shaw, F M Duncan, B C Williams, E Crichton, S A Thomson, J R E Davis, M Rademaker, C R W Edwards	160
ROLE OF ECHOCARDIOGRAPHY IN DIFFERENTIAL DIAGNOSIS OF BROAD COMPLEX TACHYCARDIA C Wren, R W F Campbell, S Hunter	166
INTERRELATION BETWEEN DONOR AND RECIPIENT HEART RATES DURING EXERCISE AFTER HETEROTOPIC CARDIAC TRANSPLANTATION S Yusuf, A Mitchell, M H Yacoub	173

PREVALENCE AND CLINICAL SIGNIFICANCE OF AORTIC VALVE PROLAPSE L M Shapiro, B Thwaites, C Westgate, R Donaldson	179
EMBOLISATION PROCEDURES IN CONGENITAL HEART DISEASE J F Reidy, O D H Jones, M J Tynan, E J Baker, M C Joseph	184
FUNCTIONAL AND ANATOMICAL CORRELATES IN ATRIAL SEPTAL DEFECT: AN ECHOCARDIOGRAPHIC ANALYSIS J C Forfar, M J Godman	193
LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION IN COMPLETE TRANSPOSITION OF THE GREAT ARTERIES WITH INTACT VENTRICULAR SEPTUM: A CROSS SECTIONAL ECHOCARDIOGRAPHIC STUDY P J Robinson, R K H Wyse, F J Macartney	201
NON-INVASIVE ASSESSMENT OF PULMONARY BLOOD SUPPLY AFTER STAGED REPAIR OF PULMONARY ATRESIA S del Torso, M J Kelly, V Kalff, G Stellin, R B B Mee, A W Venables	209
CASE REPORTS	
SPONTANEOUS RECANALISATION OF SIDE BRANCHES OCCLUDED DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY M F Shiu, A Singh	215
FLUID REMOVAL BY HAEMOFILTRATION IN DIURETIC RESISTANT CARDIAC FAILURE S H Morgan, M A Mansell, F D Thompson	218
PERMANENT PACEMAKER FAILURE DUE TO SURGICAL EMPHYSEMA S A Smith, P L Weissberg, L-B Tan	220
CHRONIC NICOTINE INGESTION AND ATRIAL FIBRILLATION P M Stewart, J R Catterall	222
CHANGING ECHOCARDIOGRAPHIC FEATURES OF A HYDATID CYST OF THE HEART W Kostucki, M van Kuyk, A Cornil	224
CORRESPONDENCE	226
NOTICES	226

Number 3

EDITORIAL: DIGITALIS: WHERE ARE WE NOW? D A Chamberlain	227
DRUG TREATMENT OF HEART FAILURE C T Dollery, L Corr	234
CHANGING DIGOXIN POTENCY AND CARDIAC MORTALITY IN ENGLAND AND WALES 1968-76 H Tunstall-Pedoe	243
RAPID PLASMA DIGOXIN ASSAY IN OUTPATIENTS—A USEFUL ROUTINE TECHNIQUE? J Savill, M Mitchell, D Wood, D M Krikler	248
WITHERING BICENTENNIAL CELEBRATIONS	251
BICENTENARY OF AN ACCOUNT OF THE FOXGLOVE A G W Whitfield	253
WITHERING AND THE FOXGLOVE: THE MAKING OF A MYTH D M Krikler	256
PLANTS AND CARDIAC GLYCOSIDES A Hollman	258
CULTIVATION AND BREEDING OF DIGITALIS LANATA IN THE NETHERLANDS C Mastenbroek	262
LEFT VENTRICULAR ANEURYSM: THE WESSEX EXPERIENCE D J M Keenan, J L Monro, J K Ross, J M Manners, N Conway, A M Johnson	269
VALVAR PROSTHETIC DYSFUNCTION: LOCALISATION AND EVALUATION OF THE DYSFUNCTION USING THE DOPPLER TECHNIQUE C Veyrat, S Witchitz, A Lessana, A Ameer, G Abitbol, D Kalmanson	273

BALLOON VALVULOPLASTY AND ANGIOPLASTY IN CONGENITAL HEART DISEASE	G A H Miller	285
ARRHYTHMOGENIC POTENTIAL OF DIURETIC INDUCED HYPOKALAEMIA IN PATIENTS WITH MILD HYPERTENSION AND ISCHAEMIC HEART DISEASE	D E Stewart, H Ikram, E A Espiner, M G Nicholls	290
USEFULNESS OF PLASMA RENIN ACTIVITY IN PREDICTING HAEMODYNAMIC AND CLINICAL RESPONSES AND SURVIVAL DURING LONG TERM CONVERTING ENZYME INHIBITION IN SEVERE CHRONIC HEART FAILURE: EXPERIENCE IN 100 CONSECUTIVE PATIENTS	M Packer, N Medina, M Yushak, W H Lee	298
EFFECTS OF ENALAPRIL IN HEART FAILURE: A DOUBLE BLIND STUDY OF EFFECTS ON EXERCISE PERFORMANCE, RENAL FUNCTION, HORMONES, AND METABOLIC STATE	J G F Cleland, H J Dargie, S G Ball, G Gillen, G P Hodsman, J J Morton, B W East, I Robertson, I Ford, J I S Robertson	305
ACUTE HAEMODYNAMIC AND METABOLIC EFFECTS OF DOPEXAMINE, A NEW DOPAMINERGIC RECEPTOR AGONIST, IN PATIENTS WITH CHRONIC HEART FAILURE	J R Dawson, D S Thompson, M Signy, S M Juul, P Turnbull, B S Jenkins, M M Webb-Peploe	313
RESPIRATORY GAS EXCHANGE IN THE ASSESSMENT OF PATIENTS WITH IMPAIRED VENTRICULAR FUNCTION	D P Lipkin, J Perrins, P A Poole-Wilson	321
CASE REPORTS		
HYPERTROPHIC CARDIOMYOPATHY SIMULATING AN INFILTRATIVE MYOCARDIAL DISEASE	A Frustaci, F Loperfido, F Pennestri	329
MANAGEMENT OF AORTIC LEFT VENTRICULAR TUNNEL	P Ribeiro, L B Bun-Tan, C M Oakley	333
RIGHT ATRIAL SPLEEN	P Kuijter, R Dion, F van Merrienboer	337
EARLY PRENATAL DETECTION OF DOUBLE OUTLET RIGHT VENTRICLE BY ECHOCARDIOGRAPHY	P A Stewart, J W Wladimiroff, A E Becker	340
NOTICE		342

Number 4

REVIEW: THE PRACTICAL IMPLICATIONS OF THE CORONARY ARTERY SURGERY TRIALS	D G Julian	343
EFFECT OF EARLY TREATMENT WITH PROPRANOLOL ON LEFT VENTRICULAR FUNCTION FOUR WEEKS AFTER MYOCARDIAL INFARCTION	M A Brown, R M Norris, P F Barnaby, G G Geary, P W Brandt	351
DIGITAL SUBTRACTION ANGIOGRAPHY IN CORONARY ARTERY BYPASS GRAFT ASSESSMENT: CLINICAL APPLICABILITY	R Hayward, G J S Hunter	357
CORONARY ANATOMY IN PATIENTS WITH VARIOUS MANIFESTATIONS OF THREE VESSEL CORONARY ARTERY DISEASE	A A Quyyumi, H K Al-Rufaie, E G J Olsen, K M Fox	362
NEW TECHNIQUE FOR SHOWING THE RELATION OF TOMOGRAPHIC MYOCARDIAL PERFUSION IMAGES OBTAINED WITH THALLIUM-201 TO THE CORONARY ARTERIES	C J Gibson, E E Laird, E D Williams, A Rajathurai, B Mittra, D Rankin	367
EFFECT OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY ON ARRHYTHMIAS COMPLICATING ANGINA	A O Molajo, G D Summers, D H Bennett	375
CHANGES IN LEFT VENTRICULAR STROKE VOLUME MEASURED BY DOPPLER ECHOCARDIOGRAPHY	H Ihlen, E Myhre, J P Amlie, K Forfang, S Larsen	378

MEASUREMENT OF MITRAL REGURGITATION BY DOPPLER ECHOCARDIOGRAPHY Y Zhang, H Ihlen, E Myhre, K Levorstad, S Nitter-Hauge	384
CORONARY ARTERY ECTASIA: ITS PREVALENCE AND CLINICAL SIGNIFICANCE IN 4993 PATIENTS G G Hartnell, B M Parnell, R B Pridie	392
AORTIC STENOSIS IN ADULTS: NON-INVASIVE ESTIMATION OF PRESSURE DIFFERENCES BY CONTINUOUS WAVE DOPPLER ECHOCARDIOGRAPHY L Hegrenæs, L Hatle	396
CONTROLLED TRIAL OF ENALAPRIL IN CONGESTIVE CARDIAC FAILURE • B P McGrath, L Arnolda, P G Matthews, B Jackson, G Jennings, H Kiat, C I Johnston	405
CAPTOPRIL MEDIATED DECREASE OF AORTIC REGURGITATION S N Reske, I Heck, J Kropp, H Mattern, R Ledda, R Knopp, C Winkler	415
ROLE OF CALCIUM IN THE INDUCTION OF CARDIAC HYPERTROPHY AND MYOFIBRILLAR DISARRAY: EXPERIMENTAL STUDIES OF A POSSIBLE CAUSE OF HYPERTROPHIC CARDIOMYOPATHY P C Pearce, C Hawkey, C Symons, E G J Olsen	420
COMPARISON OF PRIMARY PLEXOGENIC ARTERIOPATHY IN ADULTS AND CHILDREN: A MORPHOMETRIC STUDY IN 40 PATIENTS S Yamaki, C A Wagenvoort	428
PERCUTANEOUS BALLOON VALVULOPLASTY FOR PULMONARY VALVE STENOSIS IN INFANTS AND CHILDREN I D Sullivan, P J Robinson, F J Macartney, J F N Taylor, P G Rees, C Bull, J E Deanfield	435
CASE REPORTS	
RAPID EXPANSION OF A SACCULAR ANEURYSM ON THE LEFT CORONARY SINUS OF VALSALVA: A ROLE FOR EARLY SURGICAL REPAIR? R T Faillace, P Greenland, N C Nanda	442
ASSOCIATION BETWEEN POST-PERICARDIOTOMY-SYNDROME AND CORONARY OCCLUSION AFTER AORTIC VALVE REPLACEMENT I De Scheerder, M De Buyzere, D Clement	445
MANAGEMENT OF A CASE OF REFRACTORY VARIANT ANGINA WITH BENZHEXOL HYDROCHLORIDE (TRIHENXYPHENIDYL HYDROCHLORIDE) M Joy, G A Haywood, M M Webb-Peploe	448
CORRESPONDENCE	452
NOTICES	454

Number 5

BLEEDING COMPLICATIONS OF INTRACORONARY FIBRINOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION: ASSESSMENT OF RISK IN A RANDOMISED TRIAL F W A Verheugt, M J van Eenige, J C J Res, M L Simoons, P W Serruys, F Vermeer, D C A van Hoogenhuyze, P J Remme, C de Zwann, F Baer	455
SURGICAL VERSUS NON-SURGICAL MANAGEMENT OF PATIENTS SOON AFTER ACUTE MYOCARDIAL INFARCTION R W Brower, P Fioretti, M Simoons, M Haalebos, E N R Rulf, P G Hugenholtz	460
MYOCARDIAL INFARCT SIZE AND MORTALITY IN DIABETIC PATIENTS D J Gwilt, M Petri, P W Lewis, M Nattrass, B L Pentecost	466
CLASSIFICATION OF NON-Q-WAVE MYOCARDIAL INFARCTION ACCORDING TO ELECTROCARDIOGRAPHIC CHANGES H Ogawa, K Hiramori, K Haze, M Saito, T Sumiyoshi, K Fukami, Y Goto, M Ikeda	473
RECIPROCAL ST DEPRESSION IN ACUTE MYOCARDIAL INFARCTION O Odemuyiwa, I Peart, C Albers, R Hall	479

CHARACTERISTICS OF EPISODES OF ST ELEVATION OR ST DEPRESSION DURING AMBULATORY MONITORING IN PATIENTS SUBSEQUENTLY UNDERGOING CORONARY ANGIOGRAPHY	T von Arnim, B Höfling, M Schreiber	484
BYPASS GRAFTING TO THE RIGHT CORONARY ARTERY WITH AND WITHOUT ENDARTERECTOMY: PATENCY AT ONE YEAR	P H Kay, N Brooks, P Magee, M F Sturridge, R K Walesby, J E C Wright	489
QUANTIFICATION OF INTRACARDIAC SHUNTS BY GOLD-195M, A NEW RADIONUCLIDE WITH A SHORT HALF LIFE	D L Stone, R W Barber, O J M Ormerod, M C Petch, E P Wraight	495
MITRAL VALVE PROLAPSE, AORTIC COMPLIANCE, AND SKIN COLLAGEN IN JOINT HYPERMOBILITY SYNDROME	C E Handler, A Chilo, N D Light, D E Dorrance	501
EXERCISE RADIONUCLIDE VENTRICULOGRAPHY IN CHILDREN: NORMAL VALUES FOR EXERCISE VARIABLES AND RIGHT AND LEFT VENTRICULAR FUNCTION	M D Parrish, R J Boucek Jr, J Burger, M F Artman, C L Partain, T P Graham Jr	509
DIAGNOSIS AND NATURAL HISTORY OF EBSTEIN'S ANOMALY	D J Radford, R F Graff, G H Neilson	517
SPECTRUM OF CONGENITAL HEART DISEASE DETECTED ECHOCARDIOGRAPHICALLY IN PRENATAL LIFE	L D Allan, D C Crawford, R H Anderson, M Tynan	523
DESCENDING AORTOGRAPHY WITH BALLOON INFLATION: A TECHNIQUE FOR EVALUATING THE SIZE OF PERSISTENT DUCTUS ARTERIOSUS IN INFANTS WITH LARGE PROXIMAL LEFT TO RIGHT SHUNTS	P S Rao	527
ASYMMETRIC SEPTAL HYPERTROPHY AND HYPOTHYROIDISM IN CHILDREN	D I Altman, J Murray, S Milner, R Dansky, S E Levin	533
CARDIAC HYPERTROPHY, HYPERTROPHIC CARDIOMYOPATHY AND HYPERPARATHYROIDISM—AN ASSOCIATION	C Symons, F Fortune, R A Greenbaum, P Dandona	539
HYPERTROPHIC CARDIOMYOPATHY ASSOCIATED WITH A MITOCHONDRIAL MYOPATHY OF VOLUNTARY MUSCLES AND CONGENITAL CATARACT	R C A Sengers, A M Stadhouders, E van Lakwijk-Vondrovicova, K Kubat, W Ruitenbeek	543
CASE REPORT CHYLOPERICARDIUM: A RARE COMPLICATION OF A WATERSTON SHUNT	J R L Hamilton, H C Mulholland, J Cleland	548
CORRESPONDENCE		550
NOTICES		556

Number 6

EFFECTS OF MYOCARDIAL REVASCULARISATION IN PATIENTS WITH EFFORT ANGINA AND THOSE WITH EFFORT AND NOCTURNAL ANGINA	A A Quyyumi, C A Wright, L J Mockus, M Yacoub, K M Fox	557
DOPPLER ECHOCARDIOGRAPHIC MEASUREMENT OF FLOW VELOCITY IN THE ASCENDING AORTA DURING SUPINE AND UPRIGHT EXERCISE	P J Daley, K B Sagar, L S Wann	562
SINUS NODE SEQUENCES AFTER ATRIAL STIMULATION: SIMILARITIES OF EFFECTS OF DIFFERENT METHODS	W F Heddle, M E Jones, A M Tonkin	568
PREOPERATIVE AND POSTOPERATIVE PULMONARY FUNCTION TESTS IN PATIENTS WITH ATRIAL SEPTAL DEFECT AND THEIR RELATION TO PULMONARY ARTERY PRESSURE AND PULMONARY: SYSTEMIC FLOW RATIO	P M Schofield, P V Barber, T Kingston	577
CONGENITAL HEART MALFORMATIONS IN THE FIRST YEAR OF LIFE—A NECROPSY STUDY	A S Hegerty, R H Anderson, S Y Ho	583

SUBPULMONARY PLEURAL EFFUSIONS IN CHILDREN AFTER CARDIAC SURGERY

C O'Callaghan, J Cooke, I H Kerr, E A Shinebourne 593

THE HEART AND TUBEROUS SCLEROSIS: AN ECHOCARDIOGRAPHIC AND ELECTROCARDIOGRAPHIC STUDY

J L Gibbs 596

CASE REPORTS

ATRIOVENTRICULAR AND SINOATRIAL BLOCK IN THYROTOXIC CRISIS

M R Kramer, S Shilo, C Hershko 600

MYOCARDIAL TUBERCULOMA WITH RUPTURE AND PSEUDOANEURYSM FORMATION—SUCCESSFUL
SURGICAL TREATMENT

M A Halim, E N Mercer, G A Guinn 603

EFFICACY OF AN IMPLANTED AUTOMATIC DEFIBRILLATOR WHICH HAD INDUCED ATRIAL FIBRILLATION

L Jordaens, R Hamerlynck, D L Clement 605

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

609

CORRESPONDENCE

657

NOTICES

659

INDEX

660



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